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IMMUNIZATION AGAINST RHEUMATIC FEVER WITH HEMOLYTIC STREPTOCOCCUS FILTRATE

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In a previous publication,* one of us discussed the effect on thirty-four patients known to have rheumatic fever of immunization with the filtrate of N. Y. 5 hemolytic streptococcus. The results showed that during the four years of therapy 5.9 per cent of the patients suffered attacks of acute rheumatic fever with or without carditis, whereas the two control groups during the same period showed an incidence of 15 per cent and 43.4 per cent, respectively.

The results were so encouraging that we undertook the immunization of another group of children, selected at random from the Cardiac Clinic.† During the two years of treatment on which we are now reporting, two groups of patients served as controls, one for each year. In addition, one of us has re-examined the patients discussed in the previous article,‡ both treated and untreated, after the lapse of two years without further therapy, and the report on their condition will be found at the end of this article.

This paper deals primarily with the immunization of thirty-two new patients, from October, 1937, to June, 1939. During the first winter (1937-38), forty-one patients were used as controls, and, during the second winter, thirty-nine. Both the treated and the control patients were examined periodically at the Cardiac Clinic.

The only criteria for selecting the patients for treatment were their early enrollment for immunization (*September and October*) and their promise to cooperate during the protracted course of inoculations, which required, at first, weekly, and then monthly, visits to the clinic each winter, amounting to a total of from thirty-four to thirty-six visits.

*Wasson, V. P.: Immunization Against Rheumatic Fever With Hemolytic Streptococcus Filtrate, Am. Heart J. 15: 257, 1938.

†From the Department of Pediatrics, New York Post-Graduate Hospital and Medical School.

‡Through the courtesy of the Flower-Fifth Avenue Hospital, New York City.

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In this paper the clinical and laboratory observations were taken wholly from ambulatory patients, in order to exclude all data not accumulated at the clinic by us and by the same laboratory technicians.

As not all of the control patients were the same during the first and second years of observation, it is necessary to present separately

TABLE I

COMPARISON OF TREATED AND CONTROL GROUPS

		FIRST YEAR		
		TREATED		CONTROL
Number of Patients		32		41
Average Age		12.9		9
Sex	Males	19	Males	17
	Females	13	Females	24
Cardiac Class	F	4	F	4
	E + F	7	E + F	12
	I	12	I	11
	IIA	8	IIA	11
	IIB	1	IIB	3
No. of Colds per Child		2.6		1.8
Average Gain in Weight		5 lb.		3.5 lb.
Abdominal Symptoms		10+		13+
		1++		1++
		3+++		4+++
Pallor		4+		8+
		3++		2++
		4+++		12+++
Epistaxis		5+		6+
				4++
		3+++		3+++
Rheumatic Pains		5+		6+
		7++		4++
		3+++		18+++
Cardiac Symptoms		2+		5+
		1++		4++
		1+++		11+++
Headaches		4+		10+
				4++
		7+++		9+++
Twitching		2+		3+
				2++
				5+++
Severe Infections		2 Otitis Media		
No. of Attacks of Acute Rheumatic Fever, Carditis, and Chorea		3 (9.37 per cent)		18 (44 per cent)
Average E. S. R.		9.5 mm. per hr.		14 mm. per hr.
Average Hemoglobin		77.4 per cent		75 per cent
Average Nonfilamented Count		8 cells per 100		11.8 cells per 100
Results:	Excellent	7 (22 per cent)		7 (17 per cent)
	Very Good	9 (28 per cent)		3 (7 per cent)
	Good	5 (15.7 per cent)		5 (12.2 per cent)
	Average	4 (12.5 per cent)		7 (17 per cent)
	Fair	4 (12.5 per cent)		1 (2.44 per cent)
	Poor	3 (9.37 per cent)		18 (44 per cent)

Symbols: + occurred once.
++ occurred twice.
+++ occurred several times.

DISCUSSION OF TABLES

The Treated Group, between October, 1937, and June, 1938, was made up of thirty-two patients. Their average age at the outset of treatment was 12.9 years. Among them there were nineteen males and thirteen females. Eight fell in Class IIA, and one in IIB.

During the first year of treatment the average sedimentation rate was 9.5 mm. per hour, the hemoglobin, 77.4 per cent, and the Schilling, or nonfilamented, cell count, 8 cells per 100. There was an average of 2.6 colds per child. Two cases of acute exacerbation of chronic otitis media occurred, and three children, or 9.4 per cent of the treated children, suffered attacks of acute rheumatic fever, carditis, and chorea. The average gain in weight from October to June was five pounds.

Among the major subacute rheumatic fever symptoms the following occurred more than twice during the first winter: abdominal pain in three children, pallor in four, epistaxis in three, precordial pain and dyspnea in one, and headaches in seven. Mild twitchings were observed in two children at the outset of treatment.

Control Group, First Year.—Forty-one children made up the control group in 1937-38. The average age at the time of their enrollment was 9. Seventeen of the patients were boys, and twenty-four were girls. When first admitted to the group, eleven children were in cardiac Class IIA, and three in IIB. The average erythrocyte sedimentation rate, hemoglobin percentage, and nonfilament count were 14 mm. per hour, 75 per cent, and 11.8 cells, respectively. The average number of reported colds was only 1.8 per child. The average gain in weight from October until June was 3.5 pounds. Eighteen out of forty-one children suffered from attacks of acute rheumatic fever, an incidence of 44 per cent.

The subacute rheumatic symptoms were also prominent. Among the cardinal symptoms which occurred on more than two occasions were: abdominal symptoms in four patients, pallor in twelve, epistaxis in three, joint and muscle pains in eighteen, dyspnea and precordial pains in eleven, headaches in nine, and chorea in five.

The results of the second year of treatment may be summarized as follows:

Treated Group, Second Year.—At the end of the first year one patient drifted away, and observations on only thirty-one patients are available for 1938-39. Of the eight Class IIA patients in the first year, only five started as such in the second year; two had passed into Class I, and the eighth was the patient who was lost sight of. The gain in weight was 8.7 pounds per child for the twelve months. The average erythrocyte sedimentation rate was 6.9 mm. per hour, the hemoglobin, 75.3 per cent, and the nonfilament count, 6.6 per cent. There was only one attack of acute rheumatic fever, an incidence of 3.2 per cent, and the

number of upper respiratory infections per child was 2.4. All of the subacute rheumatic symptoms abated markedly. Not one patient complained of frequent abdominal or cardiac symptoms. One child remained chronically pale. One had more than two nosebleeds, two reported joint pains more than twice, and two reported frequent headaches.

Control Group, Second Year.—Among the thirty-nine children observed during the winter of 1938-39, there were seventeen females and twenty-two males. Of the thirty-nine, thirteen belonged to cardiac Class IIA, and three to IIB. The average age was 11 years, and the average gain in weight was 6.1 pounds for the twelve months. The erythrocyte sedimentation rate per child was 10 mm. per hour, the hemoglobin percentage, 72.4, and the nonfilamented count, 8.3 cells. There were three colds per child, and eleven attacks of acute rheumatic fever, chorea, and carditis in the group. Most of the eleven were hospitalized. The subacute rheumatic symptoms were many and troublesome. Among the complaints which occurred on more than two occasions there were abdominal symptoms in four, chronic pallor in fourteen, precordial pain and dyspnea in nine, epistaxis in four, joint and muscle pains in fourteen, headaches in twelve, and chorea in four.

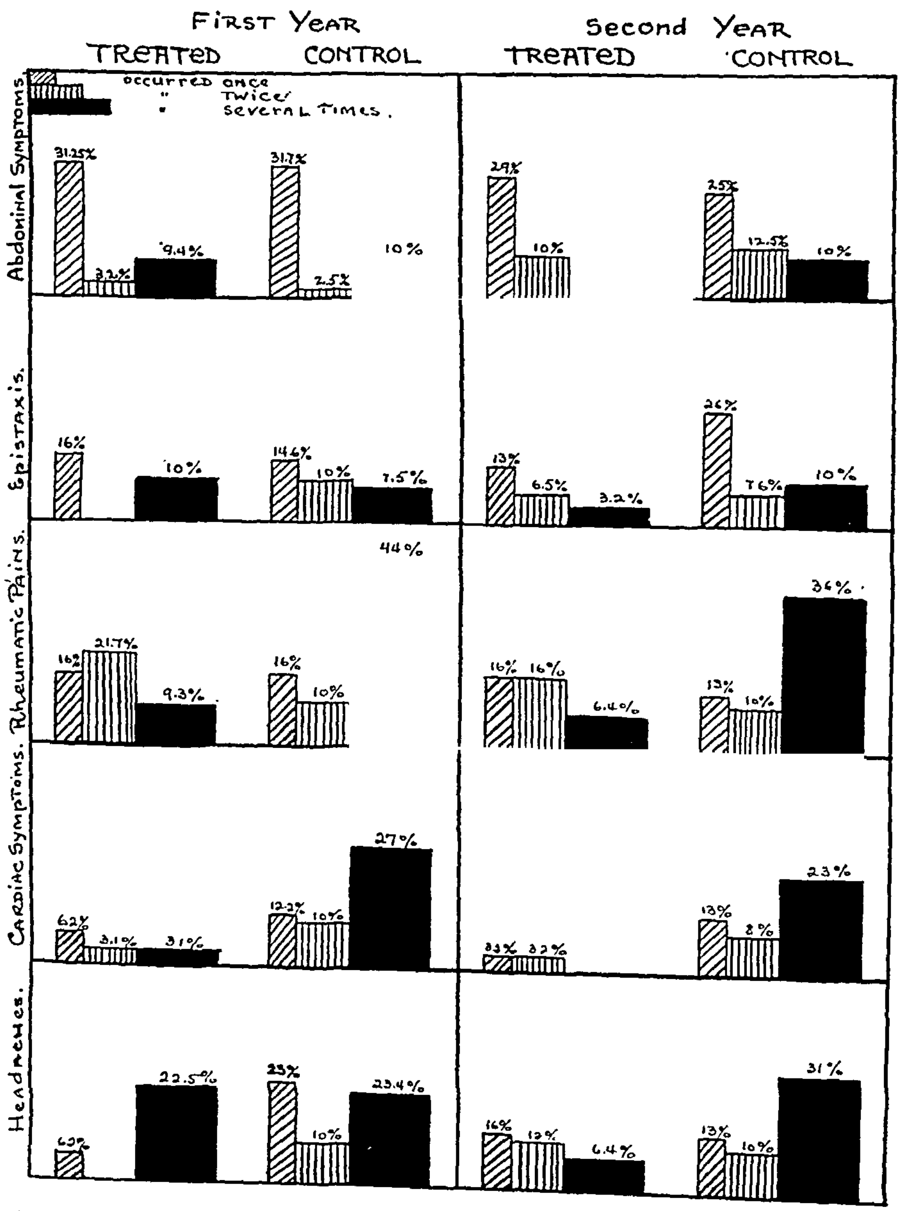
Tables I and II give our estimate of the child's health, not only from the point of view of rheumatic fever, but also by accepted health standards. In the category "Excellent," we place children who, apart from one or two transitory colds, presented no complaints and have led a normal life. Under "Very Good," we put children who had not more than one complaint, apart from usual upper respiratory infections; under "Good," those who maintained better than average good health, but could improve further. Under the term "Average," we placed children who were not really sick, yet never "really well"; under "Fair," those who were in a state of chronic ill-health, yet escaped acute illness. By "Poor," we mean all those who suffered attacks of acute rheumatic fever, as diagnosed by us and corroborated by the cardiologists. Although these categories may appear at first somewhat indeterminate, they are merely a conclusion derived from the tabulated clinical and laboratory evidence.

In Graph I we show the occurrence of common rheumatic symptoms in treated and control patients.

In our opinion, two of the most important laboratory aids in the detection of rheumatic activity are the erythrocyte sedimentation rate and the Schilling count. We found during the first year that the two tests kept in step with each other in 79 per cent of our cases. In Graph IIA we have plotted the average weekly values of the erythrocyte sedimentation rate and the nonfilamented cell counts for the two consecutive winters. From ten to forty estimations were made in each case, so that the curve gives a fair picture of the variations.

Graph II*A* shows, first, the seasonal rise and fall in rheumatic activity; second, the parallel tendency that exists between fluctuations of the erythrocyte sedimentation rate and the nonfilament count (both high normal values being taken as ten); third, the lower incidence of abnormal sedimentation rates and nonfilamented cells in the treated, as compared with the untreated, groups; and, fourth, the gradual improvement in the treated patients in the course of therapy.

Graphs II*B* and II*C* are presented to elucidate and support Graph II*A*. They show the weekly values for individual patients, one graph for the treated patients and the other for the untreated.



Graph I.—Graphic presentation of five common symptoms of rheumatic fever that occurred in treated and control patients, October, 1937, to June, 1939.

FOLLOW-UP ON FORMERLY TREATED PATIENTS

It was obviously of great interest to us to know how the patients reported in the previous paper on this subject* had fared since the treatment was discontinued, in June, 1937. The Flower-Fifth Avenue Hospital gave one of us the facilities for looking up all of the patients, treated and controls, and the results of this investigation are presented in Table III.

Table III

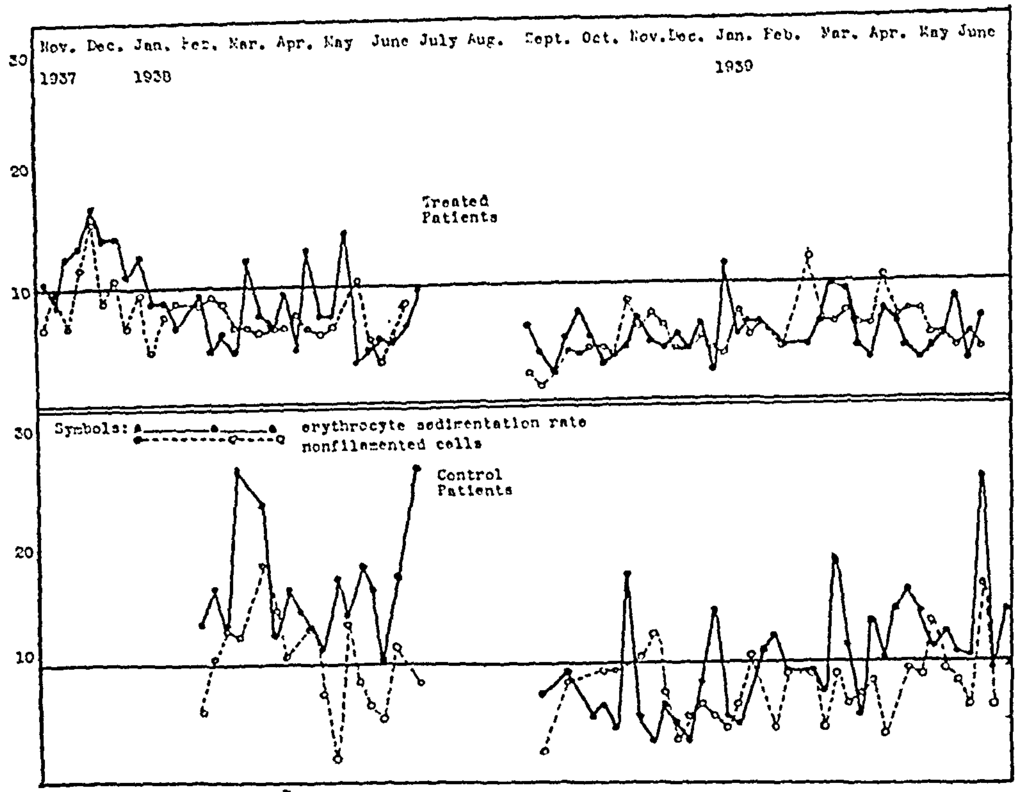
Two-Year Follow-Up of Patients at the Flower-Fifth Avenue Hospital

		TREATED	CONTROLS
		BETWEEN 1933 AND 1937	
No. of Patients Followed Up		29 out of 33	30 out of 32
Seen Personally		25	22
Seen Records		4	8
Average Age When Followed Up		12	12.6
Sex	Males	15	Males 16
	Females	14	Females 15
Average Gain in Weight		20.6 lb.	15.4 lb.
Colds, Per Child		1.8	3
Abdominal Symptoms		2+	4+
		1++	4++
		1+++	6+++
Cardiac Symptoms		2+	1+
		0	1++
		2+++	8+++
Headaches		5+	1+
		0	1++
		1+++	7+++
Epistaxis		0	4+
		1++	2++
		1+++	2+++
Rheumatic Pains		5+	3+
		1++	2++
		2+++	13+++
No. of Attacks of Acute Rheumatic Fever, Carditis, and Chorea		2 (7 per cent)	10 (33 per cent) (1 death)
Results:	Excellent	17 (58 per cent)	9 (30 per cent)
	Very Good	7 (24 per cent)	0
	Good	2 (6.9 per cent)	1 (3.3 per cent)
	Average	1 (3.5 per cent)	4 (13.2 per cent)
	Fair	0	6 (19.8 per cent)
	Poor	2 (7 per cent)	9 (30 per cent)
	Death		1 (3.3 per cent)

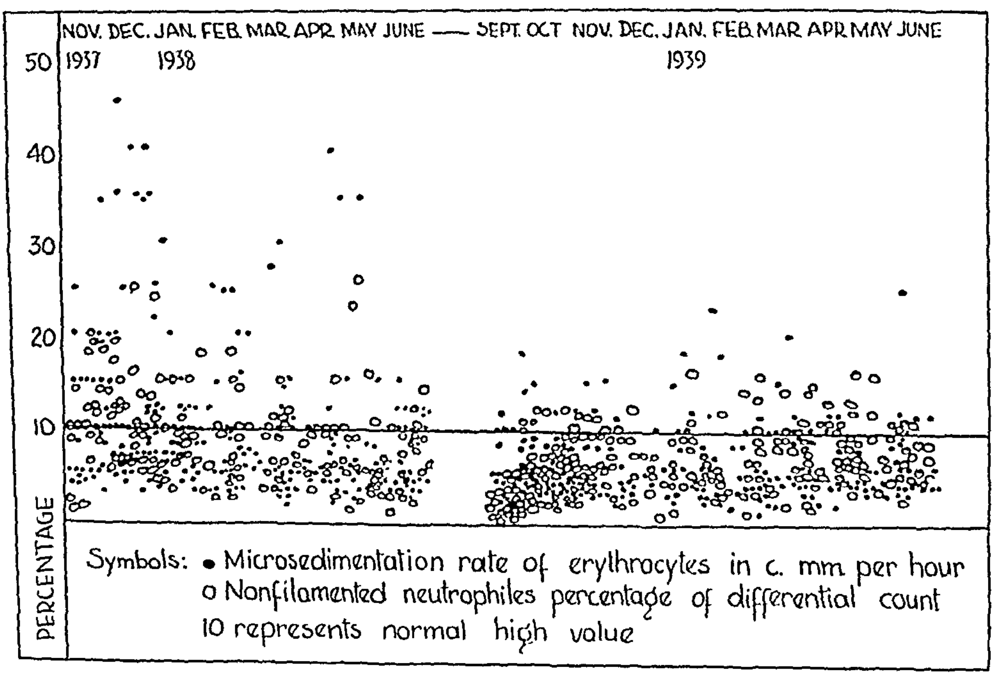
Symbols: + occurred once.
++ occurred twice.
+++ occurred several times.

We were successful in getting data on twenty-nine out of thirty-three treated children, and on thirty out of thirty-two controls. Of the previously treated patients, twenty-five presented themselves in person, and, on four others, recent cardiac clinic records were available. Of the former control patients, twenty-two came to see one of us, and the

*Supra, see first footnote, page 1.



Graph II *A*.—The average weekly values of erythrocyte sedimentation rates and nonfilamented neutrophil counts for two consecutive winters.

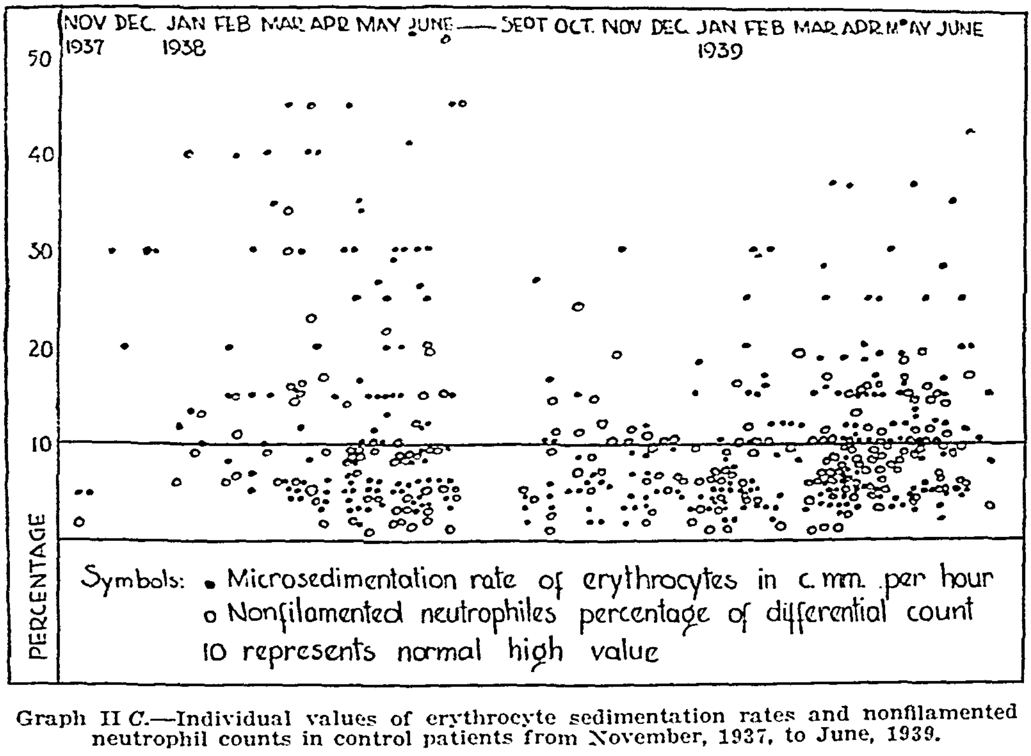


Graph II *B*.—Individual values of erythrocyte sedimentation rates and nonfilamented neutrophil counts in the treated patients from October, 1937, to June, 1939.

records of eight others contained enough recent clinical data to evaluate their state of health.

All of the treated and control patients who attended the follow-up clinic were re-examined and questioned in detail about their state of health for the preceding two years.

The average age of the previously treated patients in June, 1939 (at the time of re-examination), was 12 years, and among them there were fifteen males and fourteen females. The gain in weight for the two years was 20.6 pounds per child, and the number of colds, 1.8. Among the subacute rheumatic symptoms occurring more than twice in a given patient, there were abdominal symptoms in one, epistaxis in one, cardiac pain and dyspnea in two, headaches in one, and joint and muscle pains in two. Acute rheumatic fever recurred in two, or 7 per cent, of the patients.



Graph II *C*.—Individual values of erythrocyte sedimentation rates and nonfilamented neutrophil counts in control patients from November, 1937, to June, 1939.

The average age of the former control patients was 12.6 years. The gain in weight per child was 15.4 pounds, and the number of colds per child, three. Abdominal symptoms were prominent in six, cardiac pain and dyspnea in eight, epistaxis in two, headaches in seven, and joint and muscle pains in thirteen. There were ten attacks of rheumatic fever, an incidence of 33 per cent, with one death.

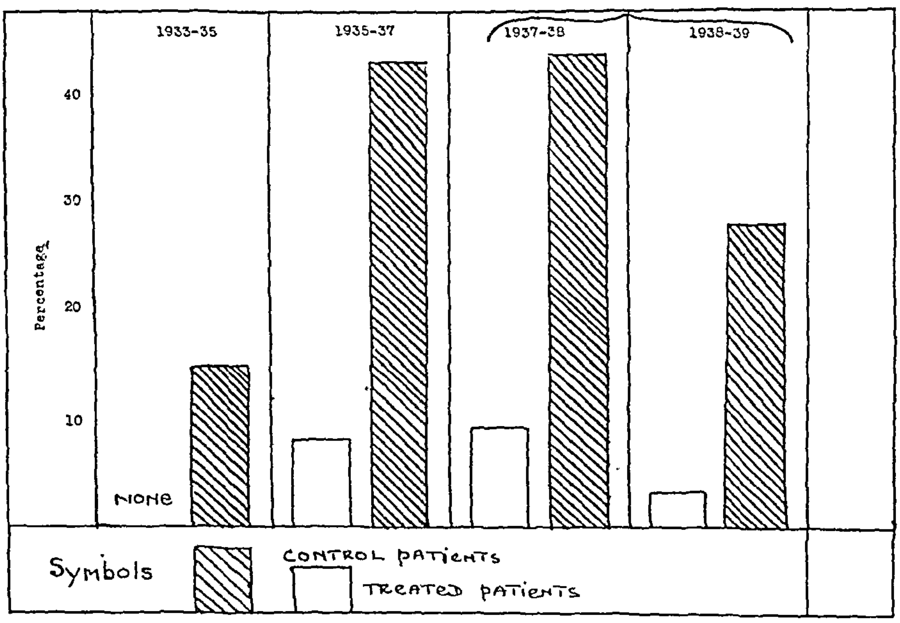
COMMENT

From the data presented here, it appears that inoculation with hemolytic streptococcus filtrate in patients known to have rheumatic fever continues, after six years, to have beneficial effects, i.e., it reduces the

number of rheumatic fever attacks, and, consequently, the incidence of carditis. Graph III summarizes the morbidity in the treated and control patients in the last six years.

Graph III shows the low relative incidence of acute rheumatic fever in the treated patients. So far as we know, the only factor extraneous to our treatment which may have contributed to the results is that the parents of perhaps half of the control patients declined to enlist their children in the treated group for the inadequate reason that they could not be bothered to send them to the clinic often enough—an indication of shiftlessness in these particular parents that manifested itself also in the general care of their children.

We realize that the total of sixty-six treated patients is too small a group from which to draw definitive conclusions. Nevertheless, the well-being of the treated patients throughout the past six years is impressive.



Graph III.—Diagrammatic presentation of comparative incidence of attacks of acute rheumatic fever in the treated and control patients between 1933 and 1939.

It is our intention to start the immunization of a new group of patients in the fall of 1939. For the past six months we have employed the pathogen selective test and the antistreptolysin titer estimation, in addition to our routine laboratory procedures,* to facilitate more precise estimation of rheumatic activity and its pathogenesis. Extensive studies on capillary resistance, blood platelets, and bleeding and coagulation time have been carried out in the last year, but since they do not cover the two-year period discussed in this article, they are not included in the results presented in this paper.

*Through the aid of a generous grant made by the John and Mary R. Markle Foundation.

THE PREDICTION OF DIFFERENCES BETWEEN PRECORDIAL LEADS CR, CL, AND CF, BASED ON LIMB LEAD FINDINGS

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OPINION is divided as to where to place the peripheral electrode in taking precordial electrocardiographic leads. There are advocates for the right arm (CR leads), the left arm (CL leads), and the left leg (CF leads), but evidence thus far available does not appear to justify a definite preference, in all cases, except from the standpoint of convenience.

The CR, CL, and CF leads differ from one another. In some patients they differ markedly. Fig. 1 illustrates this fact. In CR_4, T is inverted; in CL_4 it is upright; whereas, in CF_4, it is deeply inverted. When such marked variations are dependent on the position of the peripheral electrode, it would seem desirable to know, in advance, what they will be. In the following discussion we will show that this is possible. If the size and direction of a certain wave in any two of the three limb leads are known, its algebraic relations in the three precordial leads, CR, CL, and CF, can be predicted. To state the facts a little differently, if the size and direction of a certain wave in any two of the three limb leads are known, and if, in addition, its size and direction in one of the three precordial leads, CR, CL, or CF, are known, then its size and direction in the other two precordial leads can be predicted.

The fundamental principle which governs these predictions is not new. It is inherent in Einthoven's equation, namely, Lead I + Lead III = Lead II, as are the equations published by the Committee of the American Heart Association for the Standardization of Precordial Leads.[1] However, the practical application of this principle, for the purpose we mention, has not been emphasized.

A complete discussion of the relationships between the various precordial and limb leads could become extremely complex. It would have to consider the questions of the mode of production of action currents during activation of the cardiac muscle, the summation of these currents in the intricate aggregation of muscle bands which make up the heart, and their conduction to the body surface through tissues of various types. Fortunately, so far as our present purposes are concerned, these complex aspects of the question can be avoided. Discussion can begin with the electrical phenomena as they appear on the surface of the body. We are concerned with the differences of potential between various points on the skin, no matter how they are produced. We shall have to do with Einthoven's equation, Lead I + Lead III = Lead II, not with his controversial equilateral triangle hypothesis.

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Before going further, it might be well to dispose of one point concerning terminology, and to review certain technical features of the electrocardiograph which have a bearing on what is to follow.

(a) In the ensuing discussion, for the sake of readily designating each of the two electrodes of a given lead, we shall give the name "terminal A" to the right arm connection in Leads I and II, and to the left arm connection in Lead III. We shall give the name "terminal B" to the left arm connection in Lead I and to the left leg connection in Leads II and III. In precordial leads, as they are now taken, the peripheral electrode is connected to "terminal A," and the precordial electrode to "terminal B."

(b) The electrocardiograph is so constructed that, if terminal A is connected to the negative pole of a battery and terminal B to its positive pole, an upward deflection of the string shadow will be produced. It follows, then, that an upright wave in any standard electrocardiographic lead signifies that terminal B is connected to a point of higher potential than terminal A during the inscription of that wave. Moreover, an inverted wave signifies just the reverse, i.e., that terminal A is connected to a point of higher potential than terminal B. When the string shadow is on the base line, terminals A and B are connected to points of equal potential.

(c) Just as the direction of a wave indicates which terminal (A or B) has the higher potential, so the amplitude of the wave indicates the potential difference between them. Thus, when the instrument is standardized in the usual way, a wave of plus 2 mm. in a given lead shows that, at the time of the peak of that wave, the potential of terminal B was 0.2 millivolt higher than that of terminal A.

METHOD OF PREDICTION

According to Einthoven's law, the algebraic sum of the deviations from the base line in Leads I and III, at any given instant, will equal the deviation in Lead II, i.e., Lead I + Lead III = Lead II, or, by transposing a term, Lead I = Lead II − Lead III. It follows, then, that if the size of any deflection in Lead I is known, the algebraic difference between that deflection in Leads II and III can be predicted.

(1) *Predicting the degree of difference.*—For example, if T_1 equals plus 2 mm., T_2 and T_3 must differ by 2 mm.

(2) *Predicting the direction of difference.*—An upright T_1 signifies that the right arm is a point of lower potential than the left arm during T-wave inscription. Therefore, if leads are taken from the right arm and from the left arm to a third point, such as the left leg, using the third point as terminal B in both, the lead using the point of lower potential (right arm) as terminal A, i.e., Lead II, will have a more positive T wave than the lead using the point of higher potential (left arm) as terminal A., i.e., Lead III. *Consequently, when T_1 equals plus 2, one can predict that T_2 will be 2 mm. more positive (or less negative) than T_3.*

It is easy to prove mathematically, and to show experimentally, that this relationship between Leads I, II, and III holds good not only when electrodes are on the arms and the left leg, but when they are on

any three areas of the body surface. Thus, if the three points used are the right arm, the left arm, and a point on the precordium, making the three leads I, CR, and CL, the mathematical relationships of Einthoven's equation hold equally well. In other words, just as it is possible to predict the algebraic difference between a wave in Lead II and one in Lead III when one knows its size and direction in Lead I, so is it possible to predict the algebraic difference between a wave in CR and one in CL when one knows its size and direction in Lead I. Applying the same principle, it is possible to predict, from Lead II, the algebraic difference between a wave in CR and CF; and it is possible to predict, from Lead III, the algebraic difference between a wave in CL and CF.

Fig. 1 serves as an example of the application of this principle; T_1 is minus 3, T_2 is plus 2, and T_3 is plus 5. At the peak of the T wave, Lead I shows that the potential of the right arm is 0.3 millivolt higher than that of the left arm; Lead II shows that the potential of the right arm is 0.2 millivolt lower than that of the left leg; and Lead III shows that the potential of the left arm is 0.5 millivolt lower than that of the left leg. Rearranging these facts makes it clear that, of the three, *the left arm has the lowest potential*—0.3 millivolt lower than the right arm, and 0.5 millivolt lower than the left leg. *The left leg has the highest potential*—0.2 millivolt higher than the right arm, and 0.5 millivolt higher than the left arm. The potential of the *right arm is intermediate*—0.3 millivolt higher than the left arm, and 0.2 millivolt lower than the left leg. Consequently, of the three precordial leads, CR, CL, and CF, *Lead CL, from the left arm (the point of lowest potential) to the precordium, will show the most positive T wave.* It will be 3 mm. more positive than the T wave in a lead from the right arm to the same point on the precordium (CR), and it will be 5 mm. more positive than the T wave in a lead from the left leg to the same point on the precordium (CF). Moreover, *Lead CF, from the left leg (the point of highest potential) to the precordium, will show the most negative T wave.* T in CF will be 2 mm. less positive than T in CR, and 5 mm. less positive than in CL. And, finally, *CR will show a T wave intermediate between the other two,* i.e., 3 mm. less positive than CL, and 2 mm. more positive than CF. Reference to Fig. 1 will show that these relationships hold good for all positions of the precordial electrode. In this example, both from position *2* and position *4*, the differences are great enough to make the wave upright in CL and inverted in CF.

By the use of this method, Table I has been constructed. At the left, it shows a number of possible configurations of T in limb leads. At the right, it shows the position of the peripheral electrode (right arm, left arm, or left leg) which will give the most positive, the intermediate, and the least positive T wave.

The accuracy of these predictions has been tested in seventy cases in order to be certain that the time element did not introduce too large an error. When T waves in limb leads are large, i.e., when, during T wave inscription, potential differences between extremities are large, the results are most clear cut. When T waves in limb leads are small, the application of the principle may be obscured by small differences in string standardization, or by the phasic variation in the size of the T wave so commonly seen in precordial leads. If these extraneous factors are not carefully excluded, they often obscure the accuracy of prediction of the quantitative differences between CR, CL, and CF, even when potential differences are large.

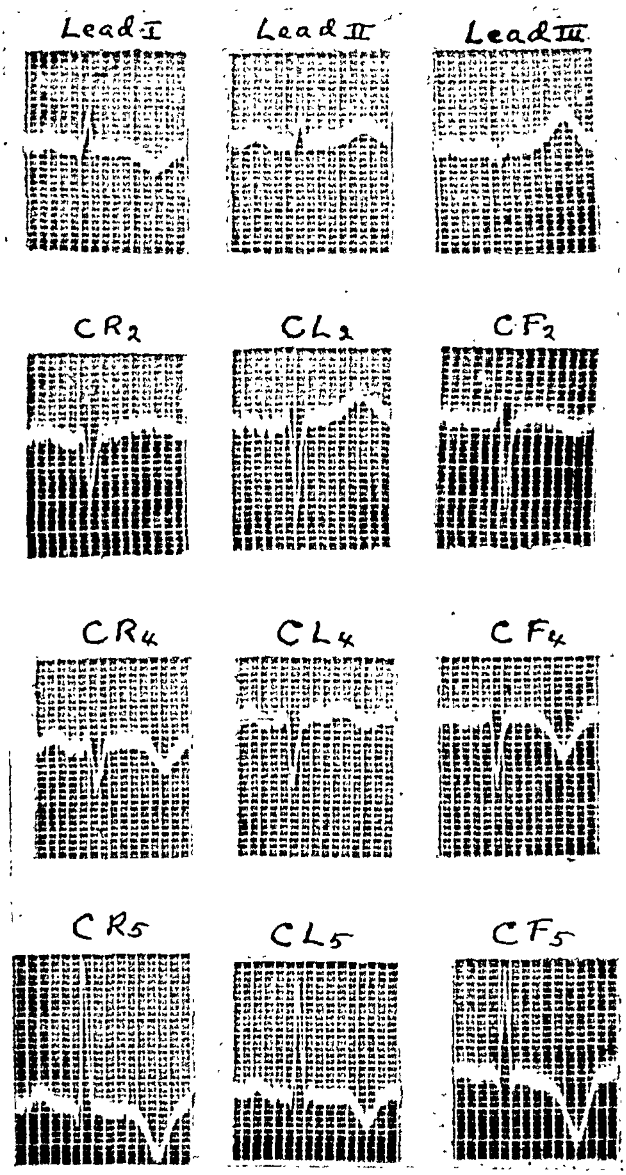

Fig. 1.—Electrocardiogram showing marked differences between the T waves in the three precordial leads, CR, CL, and CF, which are predictable from the size and direction of T in the limb leads (see Table I, Ex. 8). The details of the method of prediction are described in the text.

This method of prediction is applicable to other electrocardiographic deflections, as well as to the T wave.

The P Wave.—Table I may be used for P-wave prediction (see Fig. 2). In normals with an upright P wave in Leads I and II, CR will show the most positive P wave (see Table I, examples 1 to 4). In the average case of auricular flutter, the auricular wave has a pattern like example 7 in Table I. Consequently, CR and CL will show the most positive flutter wave.

TABLE I.

Examples	Limb Leads			When Paired with a Precordial Electrode:-*		
	T-1	T-2	T-3	The most normal (most + or least -) T wave will be obtained using the point of lowest potential, i.e.;	The intermediate T wave will be obtained by using the	The most abnormal (most - or least +) T wave will be obtained using the point of highest potential, i.e.;
(1)	2	4	2	R. arm 4	L. arm 2	L. leg 0
(2)	1	4	3	R. arm 4	L. arm 3	L. leg 0
(3)	4	4	0	R. arm 4		L. arm & L. leg 0
(4)	4	2	-2	R. arm 4	L. leg 2	L. arm 0
(5)	4	0	-4	R. arm & L. leg 4		L. arm 0
(6)	3	-1	-4	L. leg 4	R. arm 3	L. arm 0
(7)	0	4	4	R. arm & L. arm 4		L. leg 0
(8)	-3	1	4	L. arm 4	R. arm 1	L. leg 0
(9)	-4	0	4	L. arm 4		R. arm & L. leg 0
(10)	-4	-1	3	L. arm 4	L. leg 1	R. arm 0
(11)	-4	-4	0	L. arm & L. leg 4		R. arm 0
(12)	-1	-4	-3	L. leg 4	L. arm 1	R. arm 0
(13)	-2	-4	-2	L. leg 4	L. arm 2	R. arm 0

Table I.—In order to illustrate the prediction of quantitative, as well as qualitative, differences, arbitrary values have been given to the limb lead T waves, and an arbitrary value of zero has been assigned to the smallest precordial T wave (right hand column) in each example. The size of the T wave in the other two precordial leads has been calculated from these figures.

*Polarity as suggested by the Committee of the American Heart Association for the Standardization of Precordial Leads,[1] i.e., extremity electrode is electrode A; precordial electrode is electrode B.

The RS-T Segment.—Table I may also be used to predict the algebraic relations of RS-T segment deflections in CR, CL, and CF. This point will receive further discussion below.

The QRS Complex.—The same principle holds here as for the other deflections. However, during QRS inscription, movements of the string

are often very rapid. Consequently, in order to make the prediction it is necessary to have two leads recorded simultaneously in such a way as to bring out the time relations between them. Such predictions are therefore not practical for the average electrocardiographic laboratory.

The same relationship holds, if, instead of using the limbs and a precordial electrode, one applies the limb lead electrodes to any other three points on the body, and the "precordial" electrode to a fourth point. One of the experiments to illustrate this is shown in Fig. 3. The right arm electrode was applied just above the right nipple; the left arm electrode was applied just above the left nipple; and the left leg electrode was placed over the lower end of the sternum. With this set of connections, the tracing taken on Lead I (right nipple to left nipple) has a T wave of −8 mm.; the tracing taken on Lead II (right nipple to lower sternum) has a T wave of +2 mm.; and the tracing taken on Lead III (left nipple to lower sternum) has a T wave of +10 mm. Referring to the

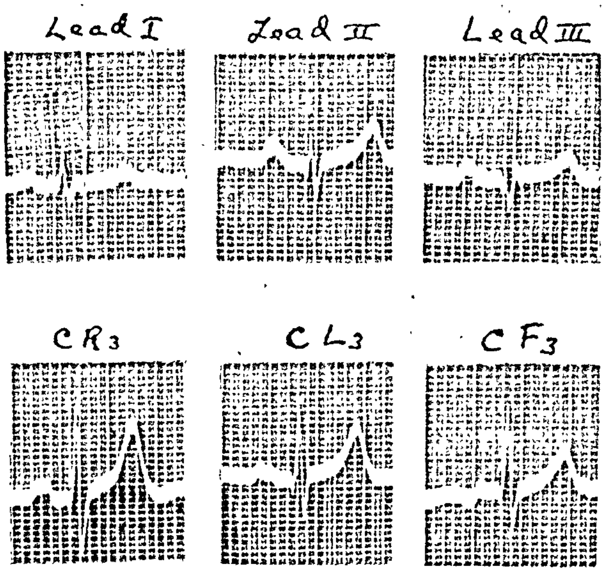

Fig. 2.—Electrocardiogram showing differences between the P waves in the three precordial leads, CR, CL, and CF, which are predictable from the size and direction of P in the limb leads. The P-wave pattern is that shown in Table I, Ex. 1.

appropriate example (i.e., No. 8) in Table I, it is clear that (1) the potential of the left nipple region is the lowest of the three; when it is paired with the fourth electrode (wherever that electrode may be placed on the body surface), it will give the most positive T wave (8 mm. more positive than the right nipple, and 10 mm. more positive than the lower sternum); (2) that the potential of the lower end of the sternum is the highest of the three, and, when paired with the fourth electrode, will give the least positive T wave (2 mm. less positive than the right nipple, and 10 mm. less positive than the left nipple; and (3) that the right nipple region has an intermediate potential, and, when paired with the fourth electrode, will give a T wave of intermediate size (8 mm. less positive than the left nipple, but 2 mm. more positive than the lower sternal

region). The experiment was done with the fourth electrode on a number of different places over the precordium and elsewhere. Fig. 3 shows the results when it was placed over the gall bladder region. Experiments were also done to study the effect of varying the position of the limb lead electrodes. Each time the predictions were verified by the tracings obtained.

These fundamental relationships might be stated in more general terms, as follows: If one chooses any three points (A, B, and C) on the body surface, and takes an electrocardiogram from A to B (Lead AB), from A to C (Lead AC), and from B to C (Lead BC), one can predict, from the size of T in any two of these three leads, which of the three points, when connected to a fourth point (P), will give the most positive T wave, which will give the most negative T wave, and which the intermediate T wave. If Lead AB shows a positive T wave, Lead AP will

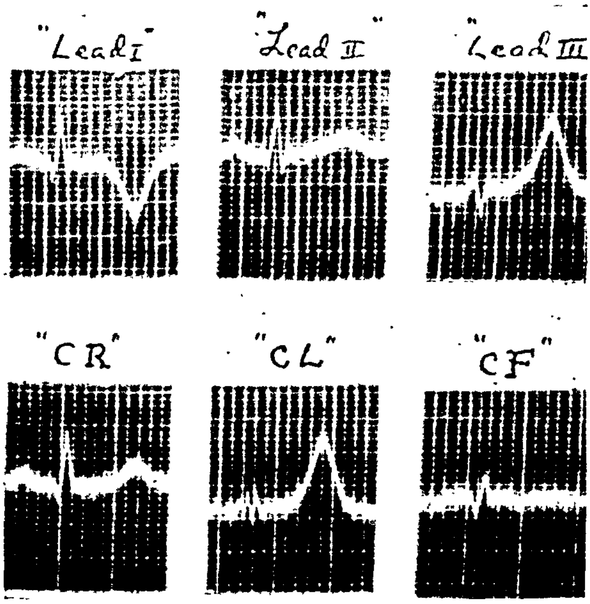

Fig. 3.—Electrocardiograms taken to show that the method of prediction described in this paper holds when the electrodes are placed on any four regions of the body surface.

The right arm electrode was placed just above the right nipple. The left arm electrode was placed just above the left nipple. The left leg electrode was placed over the lower end of the sternum. The "precordial electrode" was placed over the gall bladder.

Thus, "Lead I" is a lead from right nipple to left nipple, "Lead II" is from right nipple to lower sternum, "Lead III" is from left nipple to lower end of sternum, "CR" is from right nipple to gall bladder region, "CL" is from left nipple to gall bladder region, and "CF" is from lower end of sternum to gall bladder region. The T-wave pattern is that shown in Table I, Ex. 8.

have a more positive T wave than Lead BP. Moreover, the T wave in AP will be more positive than the T wave in BP by the amount of the size of the T wave in Lead AB. If Lead AB shows an isoelectric T wave, Leads AP and BP will have T waves of equal size. If Lead AB shows a negative T wave, Lead BP will have a more positive T wave than Lead AP. These predictions can be carried out for all possible locations of the four points. They can be verified by experiment, if one eliminates the errors to which electrocardiography is subject, i.e., differences in

string standardization, respiratory variations, and changes in position of the electrodes.

Finally, the question arises as to which of the three leads, CR, CL, or CF, is best. This cannot be answered at the present time, but the following facts may have a bearing upon the decision: (1) Patients with normal limb lead patterns (Table I, examples 1 to 4) will have the most positive T wave in CR, and the least positive T wave in CL or CF. (2) Patients with the usual limb lead pattern of acute pericarditis[2] will have the most marked elevation of the RS-T interval in CR, and the least marked elevation in CF. (3) In cases of recent posterior infarction, CF will show the most marked RS-T interval depression, and CL will

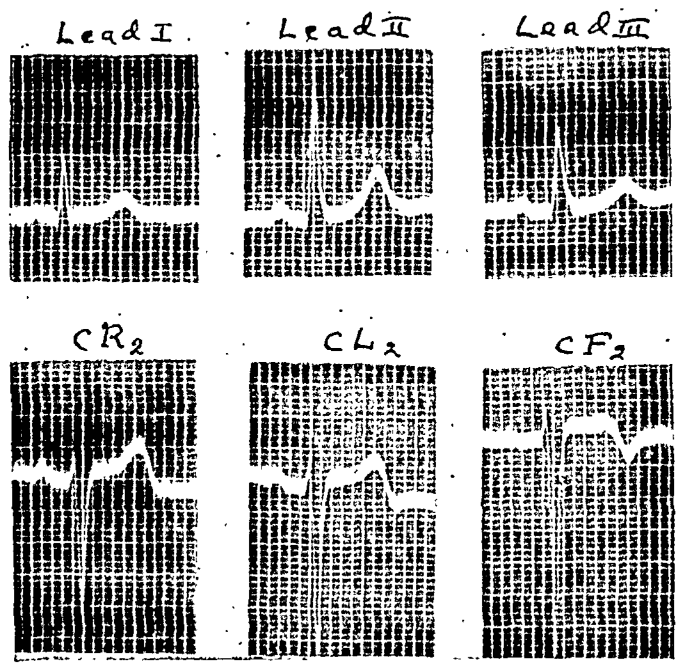

Fig. 4.—Electrocardiogram of a man, 55 years old, who had had an infarction of the anterior surface of the left ventricle four months before. At the present time the T waves are normal in the limb leads and in precordial leads CR and CL from positions 2, 3, 4, and 5. The only abnormality in T occurs in CF_3, in which there is a slight dip at the end of the wave, and in CF_2, in which there is a definite inversion. (The predictions in this tracing are shown in Table I, Ex. 1).

show the least. In cases of healed posterior infarction (Table I, examples 5 and 6), T-wave inversion will appear most frequently in CL, and least frequently in CF. (4) In cases of recent lateral infarction, CR would be most likely to show RS-T interval depression. (5) In cases of recent anterior infarction, in which the RS-T interval is elevated in Lead I, slightly depressed in Lead II, and definitely depressed in Lead III, CF will show a greater RS-T interval elevation than CR or CL. In cases of healed anterior infarction (Table I, examples 2, 7, and 8), CF will be more likely to show T-wave inversion than CR or CL.

Thus, it may be found that there is no "best lead." In one type of case, one of the extremities will be paired with the precordium, and, in

another type of case, another. At least, the choice of position for the peripheral electrode can be approached from a less empirical point of view than has been customary. One can decide whether the "*most normal*," or the "most abnormal" deflection is wanted, and place the peripheral electrode in such a way as to obtain whichever is desired.

One fact inclines us, at present, toward the use of CF as a routine lead. There is no question that the most important help obtained from precordial leads comes in the study of lesions of the anterior surface of the left ventricle. In this type of case, precordial leads often give the only electrocardiographic evidence of the patient's danger; the limb leads may be normal. In lesions located elsewhere in the heart, precordial leads might often be dispensed with, since the limb leads are likely to show diagnostic changes as well, or better. In cases of anterior infarction, in which we need help the most, CF leads are most likely to show an abnormality, both with recent and with healed lesions. In fact, cases of healing or healed anterior lesions are sometimes found in which the limb leads and the precordial leads CR and CL are normal, while the CF leads alone show T-wave inversion (see Fig. 4).

The entire question of the choice of position for the peripheral electrode must remain unsettled for the present. If CF leads are finally decided upon, for the reason just stated, there will be fewer "silent lesions." It is possible that there may be more "false positives," since normals would be most likely to show inverted T waves in CF leads. However, our studies of control groups suggest that when the precordial electrode is placed over the apex, an inverted T wave in the CF lead rarely occurs when the heart is normal.

CONCLUSIONS

1. If the size and direction of a certain electrocardiographic wave in two of the three limb leads are known, its algebraic relations in the precordial leads CR, CL, and CF can be predicted.
2. The method by which this can be done is described.
3. A table has been constructed in an attempt to simplify the process. It shows a number of limb lead patterns and the predicted differences between the T wave in the three precordial leads (CR, CL, and CF) for each pattern.
4. This table can be used to predict P-wave and RS-T interval relationships, also.
5. The principle underlying the prediction of these relationships is applicable not only when electrodes are placed on the two arms, the left leg, and the precordium, but when they are placed on any four points on the body surface.

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2. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis, J. A. M. A. 113: 1483, 1939.

STUDIES ON THE TIME REQUIRED FOR THE ELIMINATION OF QUINIDINE FROM THE HEART AND OTHER ORGANS

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Because I found that quinidine was such a valuable drug in the treatment of heart disease, and because my experience with the drug had been so successful,[1, 2] I felt that further studies on it were warranted. A series of experiments was therefore undertaken to ascertain how much time is required for the elimination of quinidine from the blood, heart muscle, and other organs.

The length of time quinidine remains in the blood was recently reported.[3] The results, in brief, were as follows:

1. When a single dose, up to ten grains, of quinidine was given intravenously to dogs, less than 6 per cent of the drug was left in the blood stream by the end of seven minutes. This corroborates the work of Weiss and Hatcher.[4]

2. When a single dose of quinidine was given orally to patients, the maximum concentration in the blood was reached in about thirty minutes, and all of the quinidine had left the blood stream by the end of one hour.

3. When repeated, small doses of quinidine were given to patients orally, the maximum concentration in the blood was reached in about one hour. All of the quinidine had left the blood stream by the end of one and one-half hours after the last dose was given.

It is the purpose of this paper to report the time required for the elimination of quinidine from the heart, lungs, liver, and other organs, after giving the drug in various amounts orally to dogs, and to present the method used in determining the amount of quinidine in the tissues and blood.

METHOD FOR THE QUANTITATIVE DETERMINATION OF QUINIDINE SULFATE IN TISSUES AND BLOOD

I. *Tissues.*—Five grams of well-ground tissue are placed in a beaker. Add sufficient distilled water (usually about 100 c.c.) to cover the material. Boil over a steam bath for about two hours, until a flocculent precipitate is formed. Add 3 c.c. of 40 per cent NaOH. Boil again over a steam bath until the volume is reduced to about 50 c.c. Place in a separatory funnel and add warm water washings from the beaker. Allow the solution to cool. Extract with ether three times,

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using about 50 c.c. each time. Shake each extraction for fifteen to twenty minutes. Evaporate the ether and dissolve the extract in water (distilled) slightly acidified with dilute H_2SO_4. Warm over the steam bath and place in the same funnel in which the ether extraction was done. Make the solution alkaline with NaOH. Extract again, three times, using 50 c.c. of chloroform each time. Shake each extraction fifteen to twenty minutes. Evaporate the chloroform from the three extractions.

Dissolve the residue in 5 c.c. of slightly acidulated water.

Take 1 c.c. of this acidulated water solution and place in a small, glass-stoppered container.

Add 2 c.c. of 0.02 normal potassium bromate solution, 0.20 Gm. of potassium bromide, and 0.25 c.c. of 4 normal HCl.

Allow to stand for ten minutes (for complete reaction between quinidine and bromine), and then add 0.3 Gm. of potassium iodide crystals.

Allow solution to stand ten minutes.

Titrate against 0.02 normal solution of sodium thiosulfate, using starch solution as an indicator.

Equation involved.—

$KBrO_3 + 5\ KBr + 6\ HCl = 6\ KCl + 3\ H_2O + 3\ Br_2$

$Br_2 + 2KI = 2\ KBr + I_2$

The addition of the 4 normal HCl to the solution containing the quinidine, potassium bromate, and potassium bromide causes a reaction between the latter two compounds which results in the liberation of free bromine. The amount of free bromine liberated is exactly equivalent to the amount of potassium bromate that was added to the solution. After the reaction between the free bromine and the quinidine is complete, the addition of 0.3 Gm. of potassium iodide takes up the excessive amount of free bromine, forming potassium bromide and liberating free iodine. The amount of free iodine present is determined by titrating against the sodium thiosulfate solution. This amount of free iodine is exactly equivalent to the amount of free bromine left over after the reaction of the bromine and the quinidine. Since the amount of free bromine liberated from a given amount of potassium bromate and the amount of free bromine remaining after its combination with the quinidine are known, it is possible, by calculating the difference between these two quantities, to determine the amount of bromine that reacted with the quinidine.

The detection of such small quantities of quinidine sulfate was made possible by the construction by Dr. A. D. Hirschfelder of a special microburette from a Kahn pipette. Amounts as small as 0.005 mg. of quinidine sulfate can be detected by this method.

It is very important that only 3 c.c. of 40 per cent NaOH solution be added to a 5-gram tissue solution, and from 15 to 18 c.c. of 40 per cent NaOH to twenty-five grams of tissue sample. There is danger of the formation of a strong emulsion, with almost a solidification of fat, from which the ether does not separate readily even after allowing the emulsion to stand for several days.

The amounts of 0.02 normal $KBrO_3$ solution, 4 normal HCl, and KBr and KI which are used in the general procedure are sufficient to detect from 0.005 to 0.2 mg. per c.c. of quinidine sulfate. For higher concentrations of quinidine sulfate these amounts should be increased accordingly.

Six milligrams of quinidine sulfate per c.c. can be estimated by this method; beyond this, the formation of a heavy precipitate after the KI is added to the solution interferes with the titration. Therefore, it is recommended that the samples be diluted to a proper concentration. If larger amounts of 4 normal HCl are used, lower yields are obtained.

II. *Blood.*—Five cubic centimeters of whole, oxalated blood are taken with a blood pipette and allowed to spread over 20 c.c. of chloroform in a separatory funnel. Twelve to sixteen drops of 30 per cent NaOH are allowed to drop over the blood surface gradually. The blood begins to char, and, upon careful shaking, it crumbles and turns into a powderlike substance. The blood is then extracted three times, using 20 c.c. of chloroform each time, after which the procedure is the same as for tissues.

Titration of Water Blanks

	Quinidine equivalent in mg./c.c.
Sample 1	+0.001
Sample 2	-0.002
Sample 3	0.000
Sample 4	+0.001

Titration of Chloroform Blanks

	Quinidine equivalent in mg./c.c.
Sample 1	+0.002
Sample 2	-0.001
Sample 3	-0.001
Sample 4	0.000

*Determination of "Unknown" Amounts of Quinidine Sulfate in Water Solution**

SAMPLE	AMOUNT PER C.C.	AMOUNT FOUND	PER CENT ERROR
1	0.02 mg.	0.0195	- 2.5
2	0.05 mg.	0.058	+16.0
3	0.08 mg.	0.076	- 5.0
4	0.01 mg.	0.0099	negligible
5	0.5 mg.	0.520	+ 4.0
6	0.005 mg.	0.0054	+ 8.0
7	0.2 mg.	0.183	- 8.5

Titration of Blanks on Blood (Human)

	Quinidine equivalent in mg./c.c.
Sample 1	+0.003
Sample 2	+0.001
Sample 3	-0.006
Sample 4	-0.001
Sample 5	+0.002

Titration of "Unknown" Amounts of Quinidine in Blood (Human)

SAMPLE	TRUE AMOUNT (MG./C.C.)	AMOUNT FOUND	PER CENT ERROR
1	0.50	0.508	+1.6
2	0.50	0.5007	negligible
3	0.50	0.489	-2.2
4	0.30	0.3024	+0.8
5	0.30	0.2934	-2.1
6	0.2018	0.2016	negligible
7	0.10	0.098	-2.0
8	0.932	0.890	-4.5

Titration of Tissue Blanks

(5 Gm. beef heart used)

	Quinidine equivalent in mg./Gm.
Sample 1	+0.001
Sample 2	+0.002
Sample 3	-0.001

*All unknowns were prepared by Dr. A. D. Hirschfelder.

TABLE I

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING SMALL, SINGLE DOSES, ORALLY (DOGS)

DOG NO.	SEX	WT. IN KILOS	ORAL DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	MG. IN TOTAL HEART	% "Q" IN HEART	WT. OF LUNG	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF KID-NEY	MG. OF "Q" PER GM WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	F	21.3	100	30 min.	171.1	0.046	7.87	7.87								
2	M	19.90	100	1 hour	186.0	0.035	6.51	6.51								
3	M	18.60	100	2 hours	174.0	0.023	4.00	4.00								
4	F	19.30	100	3 hours	143.5	0.017	2.44	2.44	243.5	0.00	645.5	0.00	107.0	0.00	51.5	0.00
5	M	20.4	100	4 hours	160.5	0.000	0.00									

Titration of "Unknown" Amounts of Quinidine in Tissue

(5 Gm. beef heart)

SAMPLE	TRUE AMOUNT (MG./GM.)	AMOUNT FOUND	PER CENT ERROR
1	0.60	0.567	-5.5
2	0.50	0.518	+3.6
3	0.60	0.592	-1.3
4	0.50	0.452	-9.6
5	0.20	0.204	+2.0

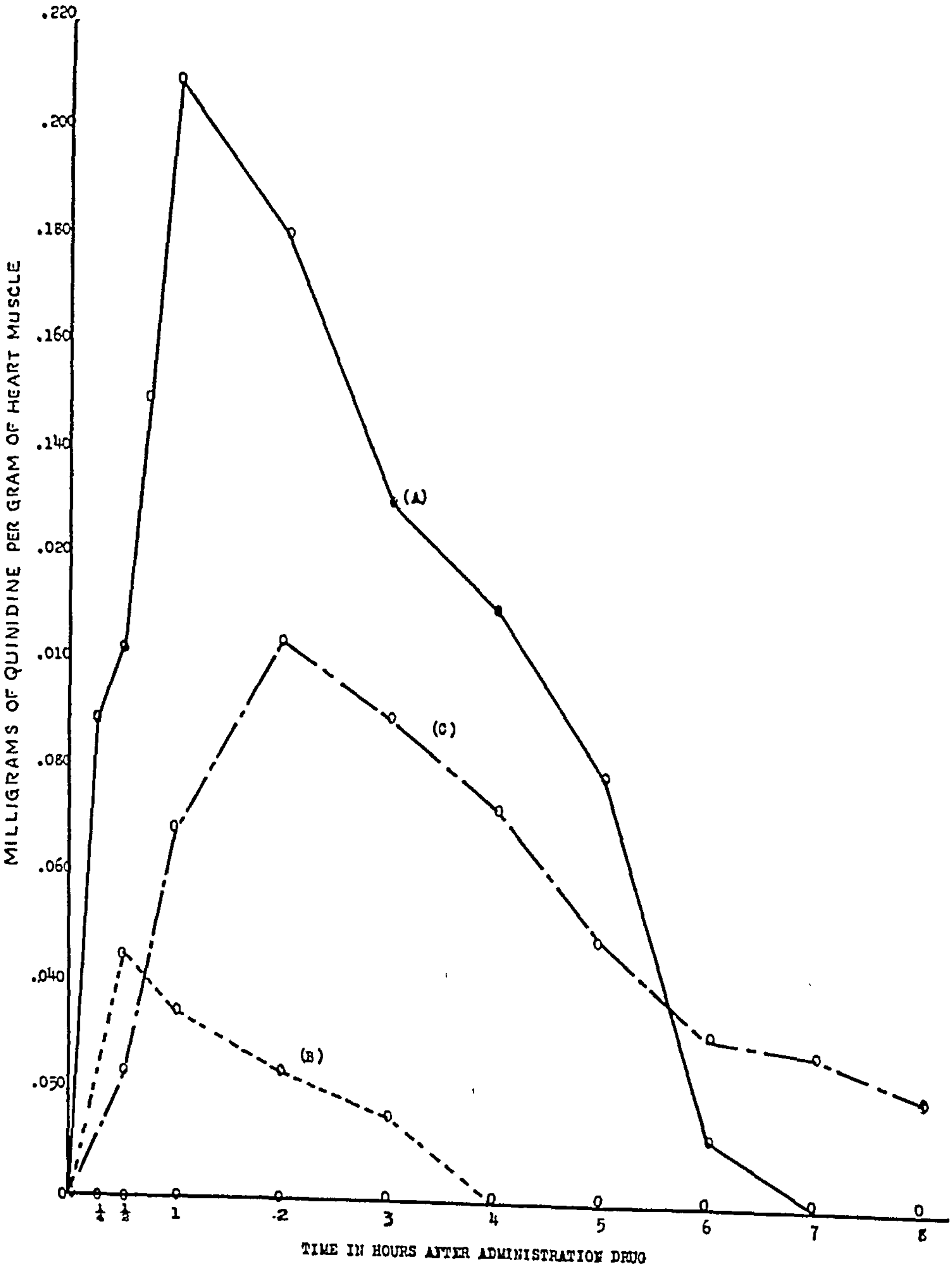

Fig. 1.—Length of time quinidine remains in the heart muscle. (*A*), After giving single, large dose—585 mg. (*B*), After giving single, small dose—100 mg. (*C*), After giving three 200-mg. doses—one hour apart (orally, to dogs).

TABLE II

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING SINGLE, LARGE DOSES, ORALLY (DOGS)

DOG NO.	SEX	WT. IN KILOS	ORAL DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	MG. IN TOTAL HEART	% "Q" IN HEART	WT. OF LUNG	MG. OF "Q" PER GM. WT.	MG. IN TOTAL LUNG	WT. OF LIVER	MG. OF "Q" PER GM. WT.	MG. IN TOTAL LIVER	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	MG. IN TOTAL KIDNEY	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.	MG. IN TOTAL SPLEEN	TOTAL % RECOVERED
1	M	20.9	585	15 min.	166.2	0.090	14.9	2.7													
2	M	20.9	585	30 min.	127.5	0.105	13.4	2.5													
3	M	16.3	585	45 min.	128.9	0.150	19.3	3.5													
4	F	15.0	585	1 hour	110.0	0.209	22.9	4.2													
5	M	21.8	585	2 hours	143.4	0.181	25.9	4.8	186.5	0.305	56.88	495.0	0.608	300.9	(1 kidney) 42.4	0.328	13.9	79.2	0.170	13.46	76.1
6	M	20.9	585	3 hours	179.3	0.131	23.4	4.3	164.5	0.140	23.03	556.5	0.445	247.6	115.7	0.052	6.0	60.5	0.088	5.32	56.5
7	M	22.3	585	4 hours	173.5	0.111	19.2	3.5	180.7	0.119	21.50	451.8	0.111	50.14	91.0	0.170	15.47	93.4	0.088	8.22	21.2
8	M	22.7	585	5 hours	162.5	0.080	13.0	2.4	193.6	0.072	13.94	488.2	0.070	34.17	84.4	0.013	1.09	92.8	0.070	6.49	12.7
9	M	20.4	585	6 hours	153.2	0.013	2.0	0.37	152.4	0.082	12.50	567.5	0.013	7.37	93.7	0.131	12.27	60.3	0.072	4.34	7.1
10	M	20.0	585	7 hours	141.1	0.000	0.0	0.00	157.1	0.056	8.80	706.1		-----	93.5	0.095	8.88	91.5	0.076	6.95	4.5

Length of time quinidine remains in the heart muscle after giving a single small dose (100 milligrams).—When a single small dose of quinidine was given orally to dogs, the maximum concentration of the drug in the heart muscle was reached in about thirty minutes. No quinidine was found in the heart muscle at the end of four hours (Table I, Fig. 1).

Length of time quinidine remains in the heart muscle after giving a single large dose (585 milligrams).—When a single large dose of quinidine was given orally to dogs, the maximum concentration of the drug in the heart muscle was reached in about one hour. It was seven hours before the quinidine had disappeared entirely from the heart muscle (Table II, Fig. 1).

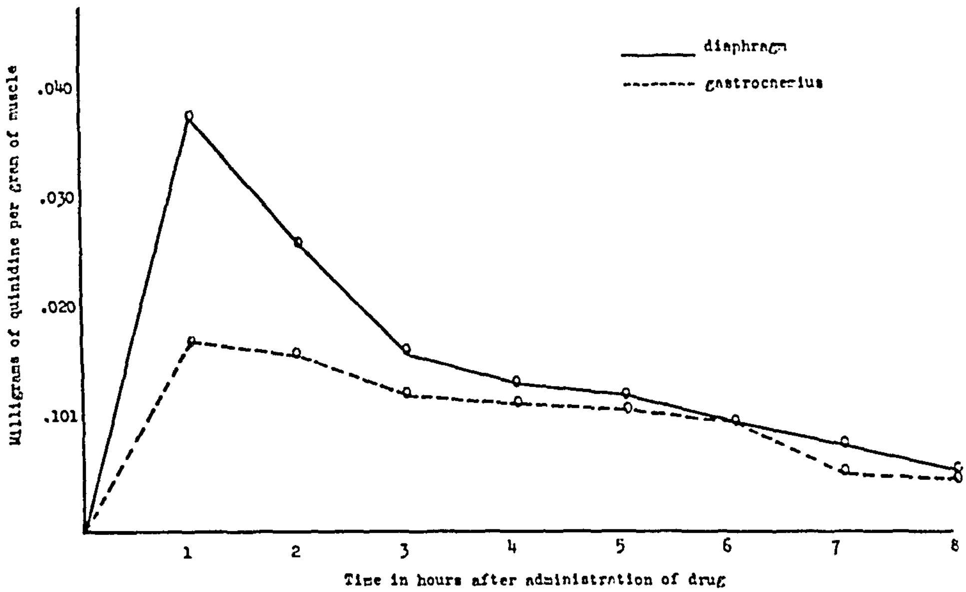

Fig. 2.—Length of time quinidine remains in diaphragm and gastrocnemius muscle after giving three 200-mg. doses, orally, one hour apart (dogs).

Length of time quinidine remains in the heart muscle after giving repeated, small doses.—When small doses (100 mg.) of quinidine were given at one-hour intervals, the maximum concentration of the drug in the heart muscle was reached in one hour when two doses were given (Table III). When three and four doses, respectively, were given at one-hour intervals, the maximum concentration of the drug in the heart was reached in two hours (Tables IV and V).

It was about six hours before the drug disappeared entirely from the heart muscle.

Length of time quinidine remains in the heart muscle after giving a single dose of 585 mg. and three 200-mg. doses one hour apart (dogs, orally).—The purpose of this experiment was to compare the length of time quinidine remains in the heart muscle when one, single, large dose is given, and when a similar amount is given, but is divided into three

TABLE III

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING TWO 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	19.1	2-100 mg.	½ hour	166.0	0.08	611.7	0.072	187.2	0.066	154.5	0.079	54.5	0.043
2	F	25.9	2-100 mg.	1 hour	266.0	0.101	845.5	0.055	281.0	0.065	178.4	0.092	54.7	0.068
3	M	20.9	2-100 mg.	2 hours	212.5	0.078	813.5	0.025	207.8	0.02	160.0	0.055	80.7	0.06
4	M	18.6	2-100 mg.	3 hours	177.5	0.04	554.0	0.013	218.0	0.015	121.2	0.023	118.7	0.017
5	M	18.0	2-100 mg.	4 hours	153.5	0.015	316.0	Traces	151.8	0.011	108.8	0.014	78.4	Traces

TABLE IV

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING THREE 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	20.4	3-100 mg.	½ hour	172.6	0.089	648.5	0.066	171.5	0.107			95.8	0.037
2	M	20.4	3-100 mg.	1 hour	200.7	0.068	507.0	0.064	192.9	0.070			123.5	0.123
3	M	19.7	3-100 mg.	2 hours	117.7	0.133	442.3	0.078	195.7	0.244			87.5	0.088
4	M	19.5	3-100 mg.	3 hours	171.0	0.093	405.0	0.088	145.5	0.058			143.7	0.085
5	M	21.6	3-100 mg.	4 hours	130.4	0.049	569.5	0.088	135.7	0.043			96.7	0.080
6	M	19.3	3-100 mg.	5 hours	154.1	0.005	476.0	0.084	188.7	0.025			94.3	0.064

TABLE V

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE AND OTHER ORGANS AFTER GIVING FOUR 100-MG. DOSES ONE HOUR APART (DOGS)

DOG NO.	SEX	WT. IN KILOS	DOSE IN MG.	TIME AFTER LAST DOSE	WT. OF HEART	MG. OF "Q" PER GM. WT.	WT. OF LIVER	MG. OF "Q" PER GM. WT.	WT. OF LUNGS	MG. OF "Q" PER GM. WT.	WT. OF KIDNEY	MG. OF "Q" PER GM. WT.	WT. OF SPLEEN	MG. OF "Q" PER GM. WT.
1	M	18.8	4-100	½ hour	165.9	0.076	470.0	0.039	202.5	0.049	97.6	0.047	119.4	0.074
2	M	19.3	4-100	1 hour	171.0	0.056	589.0	0.058	200.0	0.062	94.0	0.092	106.0	0.080
3	M	21.0	4-100	2 hours	192.5	0.088	585.0	0.082	195.0	0.099	107.5	0.142	137.0	0.088
4	F	18.2	4-100	3 hours	134.0	0.052	520.0	0.043	139.5	0.068	64.5	0.092	50.0	0.033
5	M	21.9	4-100	4 hours	190.0	0.021	717.0	0.019	173.7	0.035	92.7	0.041	229.8	0.015
6	F	25.0	4-100	5 hours	152.6	0.016	520.0	0.010	158.0	0.025	111.5	0.029	93.3	0.009

equal doses, one hour apart. When a large, single dose of quinidine is given, the height of concentration of the drug in the heart is reached in about one hour, and it is about seven hours before all of the quinidine is eliminated. When three 200-mg. doses of quinidine are given one hour apart, it takes about two hours for the drug to reach its maximum concentration in the heart muscle, and it is about nine hours before it is all eliminated (Table VI, Fig. 1). The maximum concentration of

TABLE VI

LENGTH OF TIME QUINIDINE REMAINS IN THE HEART MUSCLE, DIAPHRAGM, AND GASTROCNEMIUS MUSCLE AFTER GIVING THREE 200-MG. DOSES ONE HOUR APART, ORALLY, TO DOGS

DOG NO.	SEX	WT. IN KILOS	TIME KILLED	WT. OF HEART	MG./GM. WT.	WT. OF DIAPHRAGM	MG./GM. WT.	WT. OF GASTROCNEMIUS	MG./GM. WT.
1	M	19.7	½ hr.	162.1	0.0234		0.013		
2	M	20.4	1 hr.	195.2	0.069	97.5	0.039	92.5	0.018
3	M	18.6	2 hr.	166.2	0.105	115.2	0.026	69.5	0.016
4	M	25.0	3 hr.	257.8	0.091	147.8	0.016	93.8	0.013
5	M	19.5	4 hr.	170.0	0.074	140.6	0.0139	76.6	0.0118
6	M	16.3	5 hr.	138.0	0.049	86.7	0.0130	59.3	0.0107
7	M	19.0	6 hr.	178.7	0.032	96.4	0.010	83.5	0.01
8	M	23.5	7 hr.	172.5	0.291	97.3	0.0093	81.4	0.0062
9	M	20.0	8 hr.	127.0	0.0217	108.3	0.0061	104.6	0.0052

quinidine in the heart was about 0.209 mg. per gram of heart muscle when the single large dose was given, whereas it was only 0.105 mg. per gram of heart muscle when a slightly greater amount was given in divided doses at hourly intervals. Weiss and Hatcher,[4] Korns,[5] and Gordon, Matton, and Levine[6] have shown that a much greater amount of quinidine could be tolerated when it was divided over a period of time than when it was given in a single large dose. Lewis, Drury, Wedd, and Iliescu[7] showed that the degree of slowing of the auricular rate depended on the dose of quinidine.

Length of time quinidine remains in the lung, liver, kidney, and spleen.—Few studies were made on these organs after single, small doses were given, but it will be noticed (Table I) that at the end of four hours no quinidine was found in any of them. At the end of the fifth hour no quinidine was found in the heart muscle. It appears, then, that quinidine leaves the lungs, liver, kidneys, and spleen at about the same rate as it leaves the heart muscle, when single, small doses are given.

When a single, large dose of quinidine is given, again it appears that the maximum amount of the drug reaches these organs before the two-hour period (Table II). It may be that higher concentrations of quinidine are reached in these organs before the two-hour period. The largest amount of quinidine was taken up by the liver. The drug remained in all of the other organs longer than it did in the heart, with the exception of the liver. No quinidine was found in the liver or the heart at the end of seven hours.

Length of time quinidine remains in the heart, diaphragm, gastrocnemius and heart muscle after giving three 200-mg. doses one hour apart (dogs, orally).—The purpose of this experiment was to see whether activity of a muscle was the determining factor in the amount of quinidine taken up by that muscle. It was found that, after giving a dog three 200-mg. doses of quinidine one hour apart (Table VI), the heart took up the greatest amount of the drug; the diaphragm was next, and the gastrocnemius took up the least amount. At the end of one hour after taking the quinidine, there were 0.069 mg. of quinidine per gram of muscle in the heart, 0.039 mg. of quinidine per gram of muscle in the diaphragm, and 0.018 mg. of quinidine per gram of muscle in the gastrocnemius muscle (Table VI, Figs. 1 and 2). At the end of two hours, there were 0.105 mg. of quinidine per gram of muscle in the heart, 0.026 mg. per gram of muscle in the diaphragm, and 0.016 mg. per gram of muscle in the gastrocnemius muscle. It appears from these experiments that the more active muscles take up the greatest amount of quinidine.

Length of time quinidine remains in the skeletal muscles.—A dog weighing 9 kg. was given 585 mg. of quinidine by mouth. Three kilograms of skeletal muscle were removed from this dog one hour after the drug had been administered. The amount of quinidine per gram of muscle was found to be 0.011 mg.

Length of time quinidine remains in the liver, lungs, kidneys, and spleen after giving small doses at one-hour intervals.—After giving the dog two 100-mg. doses of quinidine one hour apart, the maximum concentration of the drug is reached in all these organs in about one hour. When three and four doses are given, it is about two hours before the concentration reaches its maximum in these organs. The drug is gradually eliminated by these organs, so that at the end of five hours very little is found (Tables IV and V). It will be noticed that the rate of absorption and elimination from the lungs, liver, kidneys, and spleen is very similar to that of the heart muscle.

SUMMARY AND CONCLUSIONS

1. After quinidine had been given orally to dogs, the rate of its absorption and elimination by the heart muscle, liver, lungs, kidneys, spleen, diaphragm, and gastrocnemius and other skeletal muscles was studied.

2. When single doses of 100 mg. were given, the maximum concentration of quinidine in the heart muscle was reached in about thirty minutes. No trace of the drug was found in the heart muscle at the end of four hours.

3. When a single, large dose of 585 mg. of quinidine was given, the maximum concentration was reached in about one hour. It was seven hours before no trace of quinidine was to be found in the heart muscle.

The lungs, liver, kidney, and spleen took up the drug at a rate similar to that of the heart, so that at the end of seven hours very little of the drug remained in any of these organs.

4. When repeated, small doses of quinidine were given at one-hour intervals, the maximum concentration of the drug in the heart was reached in about one hour when only two doses were given, and in about two hours when three and four doses were given one hour apart. Very little quinidine remained in the heart at the end of five hours. The lungs, liver, kidney, and spleen took up the drug at a similar rate, but the rate of elimination from these organs was perhaps a little slower than it was from the heart.

5. When a large, single dose of quinidine is given, the maximum concentration of the drug in the heart muscle is reached in about one hour. It is about seven hours before all of the drug leaves the heart. When the same amount of quinidine is given in three divided doses, at one-hour intervals, the maximum concentration of the drug in the heart muscle is reached in about two hours, and attains a value of not more than 50 per cent of that produced by giving a single dose. It is more than eight hours before all of the quinidine leaves the heart muscle.

6. It appears that the more active muscles absorb the most quinidine. When three 200-mg. doses of quinidine are given at one-hour intervals, at the end of one hour the heart has absorbed twice as much as the diaphragm, and the diaphragm twice as much as the gastrocnemius muscle.

7. A method is presented for the extraction and quantitative determination of the quinidine content of the blood and tissues.

I should like to take this opportunity to express my thanks to Dr. A. D. Hirschfelder, of the Department of Pharmacology, University of Minnesota, for his many helpful suggestions and practical aid in carrying out the work reported in this paper; also, to Mr. G. Tamcales, for his assistance in carrying out the laboratory studies.

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RESPONSES OF THE NORMAL HEART AND THE HEART IN EXPERIMENTAL VITAMIN B_1 DEFICIENCY TO METABOLITES (PYRUVIC ACID, LACTIC ACID, METHYL GLYOXAL, GLYCERALDEHYDE, AND ADENYLIC ACID) AND TO THIAMIN*

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PREVIOUS study on rats[1] has demonstrated changes in the heart rate and electrocardiographic complexes, as well as in the responses to drugs, in vitamin B_1 deficiency. This work has now been extended in order to seek the cause of these abnormalities in deficient animals. Disturbances of the intermediary carbohydrate metabolism of the cells of the body are believed to occur in this deficiency, since the lack of vitamin B_1 prevents the normal disposal of pyruvic acid and, indirectly, of lactic acid. In vitamin B_1 deficiency these and other metabolites accumulate in the body.[2, 3, 4, 5, 6, 7] The question, therefore, has been raised whether the symptoms and physiologic changes in vitamin B_1 deficiency are caused by a failure of tissue metabolism, per se, or by the accumulation of toxic products resulting therefrom. The effects of the latter have been investigated. By the administration of various metabolites we have attempted either to produce in normal rats electrocardiographic or other changes characteristic of vitamin B_1 deficiency, or to precipitate in partially deficient rats a severely deficient state. It was also considered desirable to obtain information on the pharmacology of these metabolites.

METHOD OF INVESTIGATION

The preparation of a diet deficient in vitamin B_1 and the method of taking electrocardiograms have been described previously.[1] In this investigation, the yeast in the deficient diet was treated with 0.1 N sodium hydroxide and autoclaved (15 pounds pressure) for six hours at a pH of 7 to 8. In part of the work, washed casein† was used without rewashing. Rats were kept for long periods on the deficient diet; each time that the decrease in heart rate and weight indicated that the rats were moderately deficient, they were given subcutaneous injections of synthetic crystalline vitamin B_1‡ (thiamin hydrochloride). Fresh dilutions of 1 to 50 or 1 to 100 were made up daily from 0.1 per cent stock solu-

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†Obtained from A. H. Thomas Company.

‡Usually Betaxin (Winthrop) was used; in a few cases it was Betabion (Merck). Both were generously supplied for this work.

tions. Doses of 0.016 mg. regularly brought about a rapid increase in heart rate and weight. The number of days between such doses is only a rough estimate of the maintenance period for this amount of thiamin because of the difficulty of bringing rats to the same state of deficiency before each dose. Control rats were fed either a control diet, similar to the deficient diet but containing unautoclaved yeast, or a diet of bread and milk supplemented by cod-liver oil, iron ammonium citrate, and yeast.

Standardized electrocardiograms were recorded on paper, which was run at a speed of 100 mm. per second in order to allow analysis of the complexes. In records of normal rats the T waves have usually been found to be upright or flat in Lead I, and upright in Leads II and III. In rats, T_1 is usually very low. Only changes of more than thirty beats per minute in the heart rate, or 1 mm. in the height of the T waves, have been accepted as being outside normal limits. A few experiments, in which irregular variations of more than thirty beats appeared, have been designated as showing no change in heart rate. Only marked changes in the height of the origin of the T waves have been noted, since considerable variation caused by movement or other factors has been observed in control records on normal rats.

In order to determine the sensitivity and cardiac response of normal rats and of rats deficient in vitamin B_1 to various metabolites, three types of experiments were performed on each group of animals: (1) The fatal doses of the substances under investigation were determined approximately, using various routes of administration. In some cases, however, the amount of chemical material and the number of deficient rats available did not permit extensive trials. (2) Short experiments were carried out in which electrocardiograms were recorded before, and at frequent intervals for several hours after, the administration of smaller doses of the metabolites. Rats kept on a diet deficient in vitamin B_1 were usually used when they were not in a severely deficient state, that is, when the heart rate had fallen to 300 to 400 beats per minute and before neurologic symptoms had disappeared.

(3) Longer experiments were performed, in which 1 to 3 doses of the metabolite studied were administered daily over a period of several weeks. At intervals of several days, or oftener, if necessary, electrocardiograms were recorded before, and for a few hours after, the daily doses. In a number of experiments the body weight and food intake were also measured. In deficient rats the heart rate or body weight, or both, have been used as criteria for judging the speed with which rats became deficient and the severity of the deficiency.

Doses of the substances administered were always expressed in terms of milligrams per 100 grams of body weight. Pyruvic,* lactic,† and adenylic‡ acids were neutralized with sodium hydroxide to pH 7, and diluted to contain a desired percentage of acid by weight. The strength of the solutions used depended on the amount to be given and on the route of administration. When administered orally the solutions were given by means of a small woven catheter, used as a stomach tube. A small series of intravenous injections were made into the exposed femoral vein, with or without ether anesthesia.

Pyruvic and lactic acids were studied somewhat more extensively than other metabolites, because of evidence in the literature relating them to vitamin B_1 deficiency. Experiments on methyl glyoxal, glyceraldehyde, and adenylic acid were also carried out, as well as certain control experiments, using sodium bicarbonate, ammonium chloride, and glucose. Additional observations on the cardiac effect of

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*Obtained from Eastman Kodak Company.

†Baker's Analyzed.

‡Prepared and purified by Dr. F. P. Nabenhauer, of the Smith, Kline, and French Laboratories.

large doses of vitamin B_1, as well as of the lack of certain vitamins other than B_1, were also made.

RESULTS

Pyruvic Acid ($CH_3.CO.COOH$)

Vitamin B_1 has been regarded as a catalyst which brings about the oxidation of pyruvate in brain tissues.[5] Pyruvic acid has been found in increased amounts in the blood of rats and of pigeons deficient in vitamin B_1,[2, 9] as well as in patients with "wet" beriberi.[3, 7] Lu[10] has shown that the blood pyruvate values in rats rose progressively as the heart rate fell. It has not been definitely proved, however, that the presence of pyruvic acid is responsible for the symptoms of polyneuritis.[11] The effects of injecting pyruvate into animals and man have been discussed by Wilkins, Weiss, and Taylor,[12] who administered sodium pyruvate orally and intravenously to normal subjects and to patients with beriberi. In the latter group they found that the sodium pyruvate tolerance curve was occasionally increased in height, but a definite deviation from the normal was not observed. In normal and deficient persons, electrocardiograms after giving sodium pyruvate showed lengthening of the Q-T interval and a minor, but definite, decrease in the amplitude of the T waves. These temporary changes were probably caused, at least in part, by alkalosis. Kalaja and Närvanen[13] found that the subcutaneous injection of pyruvic acid decreased the heart rate of rats, but not of pigeons and rabbits, and that this effect was somewhat greater than that produced by lactic acid. Lu[10] observed no change in the heart rate of rats and rabbits after the intravenous injection of pyruvate in doses producing blood pyruvate levels which were above the highest occurring in vitamin B_1 deficiency.

Sodium Pyruvate, Administered Orally.—Two normal rats developed marked diarrhea, but recovered, after doses as high as 713 and 800 mg. per 100 grams of body weight. The fatal dose for deficient rats was approximately 600 mg. (Table I). In normal and deficient rats which received smaller single doses of pyruvate the heart rate remained unchanged, but in two out of four deficient rats the T waves were higher, or had a higher origin, after pyruvate (Table II).

TABLE I

FATAL DOSES OF CHEMICAL SUBSTANCES FOR NORMAL AND DEFICIENT RATS

	ORALLY		SUBCUTANEOUSLY	
	NORMAL RATS	DEFICIENT RATS	NORMAL RATS	DEFICIENT RATS
	(MG. PER 100 GRAMS BODY WT.)		(MG. PER 100 GRAMS BODY WT.)	
Sodium Pyruvate*	Over 800	600	275-300	150-175
Pyruvic Acid	300	350	--	--
Sodium Lactate*	500-700	Over 700	350-400	Over 450
Lactic Acid	550	Over 500	--	--
Methyl Glyoxal	175-200	Over 200	--	--
Glyceraldehyde	Over 600	Over 600	--	--

*Expressed as mg. of acid per 100 grams of body weight.

TABLE II

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF SODIUM PYRUVATE AND PYRUVIC ACID

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE* (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE			NUMBER OF RATS AND EFFECT ON T WAVES			REMARKS
				INCREASE	NO CHANGE	DECREASE	INITIAL FORM OF T WAVES	NO CHANGE	FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	
Sodium Pyruvate p.o.	Normal	4	200	0	4	0	4, T_2 & T_3 upright	4	Unchanged	
	Deficient	4	175-225	0	4	0	3, T_2 & T_3 upright	2	1, T_2 & T_3 higher with high origin	
							1, flat or low	0	1, upright	
Sodium Pyruvate s.c.	Normal	6	96-150	1 (slight)	4	1 (slight)	6, T_2 & T_3 upright	5	1, T_3 flat	
	Deficient	8	100-135	2 (slight, transient)	2	6	2, upright	0	2, T_2 & T_3 higher	Before vitamin B_1
							6, T_2 or T_3 low, flat or inverted	0	6, upright or higher	
	Deficient after Vitamin B_1	3	125	0	3	0	1, upright	0	1, T_2 higher	14-21 hours after 0.015 mg. vitamin B_1
							2, flat or inverted	1	1, T_2 & T_3 upright	
Sodium Pyruvate i.v.	Normal	2	100	0	0	2	1, T_2 & T_3 upright	1	Unchanged	Ether anesthesia
							1, T_3 flat	1	Unchanged	
	Deficient	2	75-100	0	2	0	1, T_2 & T_3 upright	0	1, T_2 & T_3 slightly higher	
							1, flat or inverted	0	1, T_2 & T_3 upright	
Pyruvic Acid p.o.	Normal	7	56-182	0	4	3	7, T_2 & T_3 upright	4	2, T_2 slightly higher 1, T_2 slightly lower	Few electrocardiograms in some cases
	Deficient	7	50-100	2	4	1	3, T_2 & T_3 upright	3	Unchanged	
							3, low, flat or inverted	2	1, lower	

*In terms of pyruvic acid.

TABLE III

ELECTROCARDIOGRAPHIC CHANGES IN NORMAL RATS AFTER REPEATED DOSES OF CHEMICAL SUBSTANCES

	NO. OF RATS	DOSAGE (MG. PER 100 GRAMS BODY WT.)	DURATION OF EXPERIMENT (DAYS)	NUMBER OF EXPERIMENTS AND EFFECT ON HEART RATE		NUMBER OF EXPERIMENTS AND EFFECT ON T WAVES	
				AFTER INDIVIDUAL DOSES†	DURING EXPERIMENTAL PERIOD‡	AFTER INDIVIDUAL DOSES	DURING EXPERIMENTAL PERIOD
Sodium Pyruvate p.o.	6	85-656*	16-26	13, no change 4, slight decrease	4, no change 2, slight decrease	16, no change 1, T_2 higher	6, no change
Sodium Pyruvate s.c.	2	64-151*	4-12	2, no change	1, no change 1, slight decrease	2, no change	2, no change
Pyruvic Acid p.o.	5	61-200	8-14	6, no change 4, decrease	2, no change 3, decrease	7, no change 3, T_2 or T_3 slightly higher	5, no change
Sodium Lactate p.o.	6	182-648*	18-21	6, no change 2, slight decrease	5, no change 1, decrease	8, no change	6, no change
Sodium Lactate s.c.	2	64-358*	15	Variable, few records	1, no change, variable 1, decrease	3, no change 1, T_2 & T_3 higher	2, no change
Lactic Acid p.o.	2	68-329	4-12	3, no change 1, slight increase 2, decrease Few electrocardiograms	1, no change 1, decrease	5, no change 1, T_2 slightly higher	1, no change 1, slightly lower
Methyl Glyoxal p.o.	3	100-200	10-19	6, no change 1, increase 1, decrease	2, no change 1, decrease in 1 record	8, no change	2, no change 1, slightly lower
Glyceraldehyde p.o.	3	400	15-22	7, no change 3, slight decrease	2, no change 1, slight decrease	10, no change	2, no change 1, T_3 slightly higher

*In terms of pyruvic or of lactic acid.
†Only changes of 30 beats or more are noted.
‡Only changes of 40 beats or more are noted.

Control rats which received repeated daily doses of pyruvate by mouth showed but few changes in the heart rate or in the shape of the T waves (Table III). Young control rats grew rapidly, and older rats, with one exception, maintained their weight during the administration of pyruvate. On these rats, weekly experiments were performed in which electrocardiograms were taken before, and at hourly intervals for three hours after, the administration of 200 mg. of pyruvate. The records showed only an occasional increase in the height of the T waves or a slight decrease in rate after pyruvate. Qualitative tests by a modification[14] of the method of Simon and Piaux[15] indicated that the urine contained pyruvic acid most of the time during the period that pyruvate was being administered.

One additional normal rat was fed a control diet, but was restricted to the average amount of food usually consumed by deficient rats. This rat decreased in weight, but maintained a normal heart rate. After seventeen days it was continued on the same food intake, but for 12 days received, in addition, 400 mg. of sodium pyruvate daily by mouth. The heart rate and electrocardiogram did not change significantly. The body weight continued to decrease.

Deficient rats which were receiving daily doses of sodium pyruvate by mouth rapidly increased in weight after the administration of 0.016 mg. of vitamin B_1, as did control deficient rats which were not receiving sodium pyruvate. Measurement of the food intake for a period of eight days indicated that the administration of the pyruvate solution by

TABLE IV

EFFECT ON RATS DEFICIENT IN VITAMIN B_1 OF REPEATED DOSES OF CHEMICAL SUBSTANCES

	NO. OF RATS	DOSES (MG. PER 100 GRAMS BODY WT.)	DURATION OF EXPERIMENT (DAYS)	AVERAGE NO. DAYS MAINTAINED ON 0.016 MG. VITAMIN B_1	
				CONTROL	DURING EXPERIMENT
Sodium Pyruvate p.o.	1	125-200*	13	--	11
	4	300-400*	25-43	9.5	8
Sodium Pyruvate s.c.	5	100-200*	10-15	8.5	8
Pyruvic Acid p.o.	2	50-125	9	6.5	6
Sodium Lactate p.o.	2	400*	18	6	6
Sodium Lactate s.c.	2	100-200*	13	--	--
Lactic Acid p.o.	2	200-400	10-18	7.5	6
Methyl Glyoxal p.o.	5	100-300	8-20	8.5	8.5
Glyceraldehyde p.o.	3	400	14-21	8	11

*In terms of pyruvic or of lactic acid.

stomach tube did not significantly influence the normal food intake. Two rats which were receiving pyruvate were maintained on 0.016 mg. of thiamin for a somewhat shorter time, and one for a slightly longer time, than when they were not receiving pyruvate (Table IV). Dropped beats

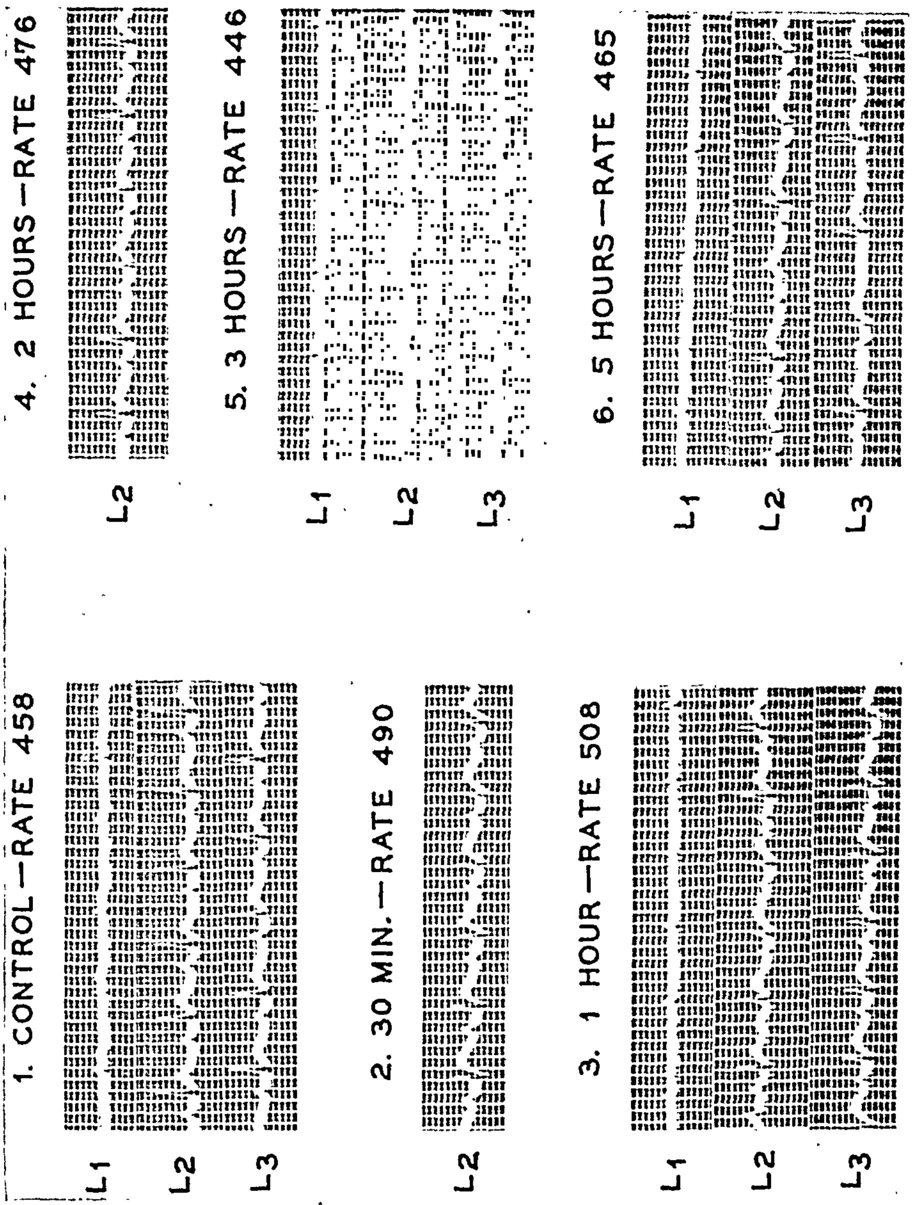

Fig. 1.—Electrocardiograms of a normal rat before and after the subcutaneous injection of 125 mg. of sodium pyruvate per 100 grams of body weight. The time lines are 1/50 second apart.

and sinoauricular block, which are seldom observed in the electrocardiograms of rats, appeared occasionally in those of three deficient rats which were receiving daily doses of pyruvate. The abnormal T waves and sinus arrhythmia which occur in vitamin B_1 deficiency appeared frequently, and the complexes varied considerably after vitamin B_1. In two rats, electrocardiographic abnormalities persisted even after frequent small doses of thiamin which brought about progressive weight gains. In these rats the electrocardiograms did not become normal for some time after pyruvate was discontinued. The pH of the urine did not differ

greatly after pyruvate (6.4 to 7.0) from that of control (6.4 to 6.8) or deficient rats (5.7 to 7.8) which had not received pyruvate.

Sodium Pyruvate, Administered Subcutaneously.—The fatal subcutaneous dose of sodium pyruvate was lower for rats deficient in vitamin B_1 (150 to 175 mg.) than for normal rats (275 to 300 mg.) (Table I). Two deficient rats which died from two and one-half to four hours after the adminstration of 150 mg. of pyruvate developed neurologic symptoms before death. Smaller single doses produced no significant changes in the electrocardiograms of normal control rats (Table II, Fig. 1). In deficient rats, sodium pyruvate was often followed by a decrease in heart rate, sometimes preceded by a temporary rise (Fig. 2). The T waves became upright, or higher, if already upright (Table II, Fig. 3). If the pyruvate was given from fourteen to twenty-one hours after the administration of thiamin, the decrease in rate after pyruvate was less marked than before thiamin, but the T waves were higher in two cases (Table II, Fig. 2). Three deficient rats were given 4 mg. of *atropine sulfate* per 100 grams of body weight, followed by 125 mg. of pyruvate. In these rats the rate remained unchanged, but the T waves were higher

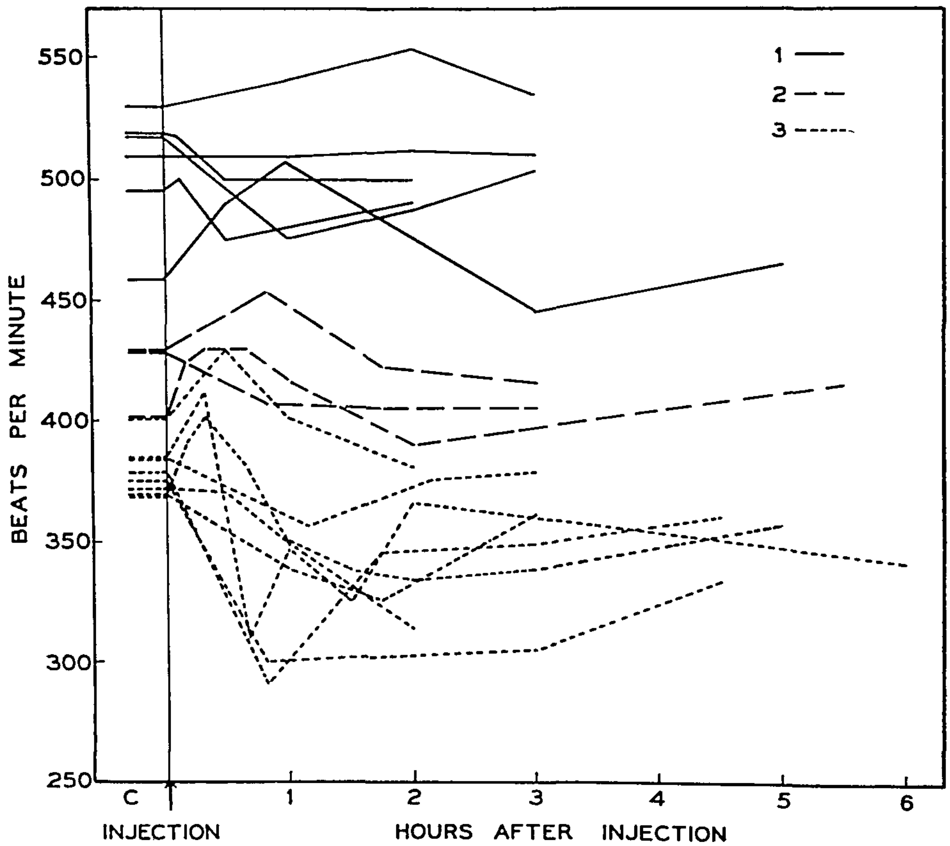

Fig. 2.—Effect on heart rate of the subcutaneous injection of from 96 to 150 mg. of sodium pyruvate per 100 grams of body weight. Results have been plotted on (*1*) normal rats, (*2*) rats on a diet deficient in vitamin B_1 which had received thiamin seventeen to twenty-one hours previously, and (*3*) rats on a diet deficient in vitamin B_1.

in one case, indicating that the fall in heart rate usually observed after pyruvate, but probably not the T-wave changes, is caused by vagal stimulation.

Tables III and IV summarize the effects of repeated, small, daily doses of sodium pyruvate, injected subcutaneously into control and deficient rats. While receiving pyruvate, the majority of the deficient rats with low or flat T waves did not show any change in the T waves after the doses of vitamin B_1 which they received. Since few other significant changes were observed, and since repeated subcutaneous injections of pyruvate caused considerable local irritation in the rats, no further experiments were performed.

Sodium Pyruvate, Administered Intravenously.—The fatal dose was not determined, but one control rat died after 121 mg. had been injected.

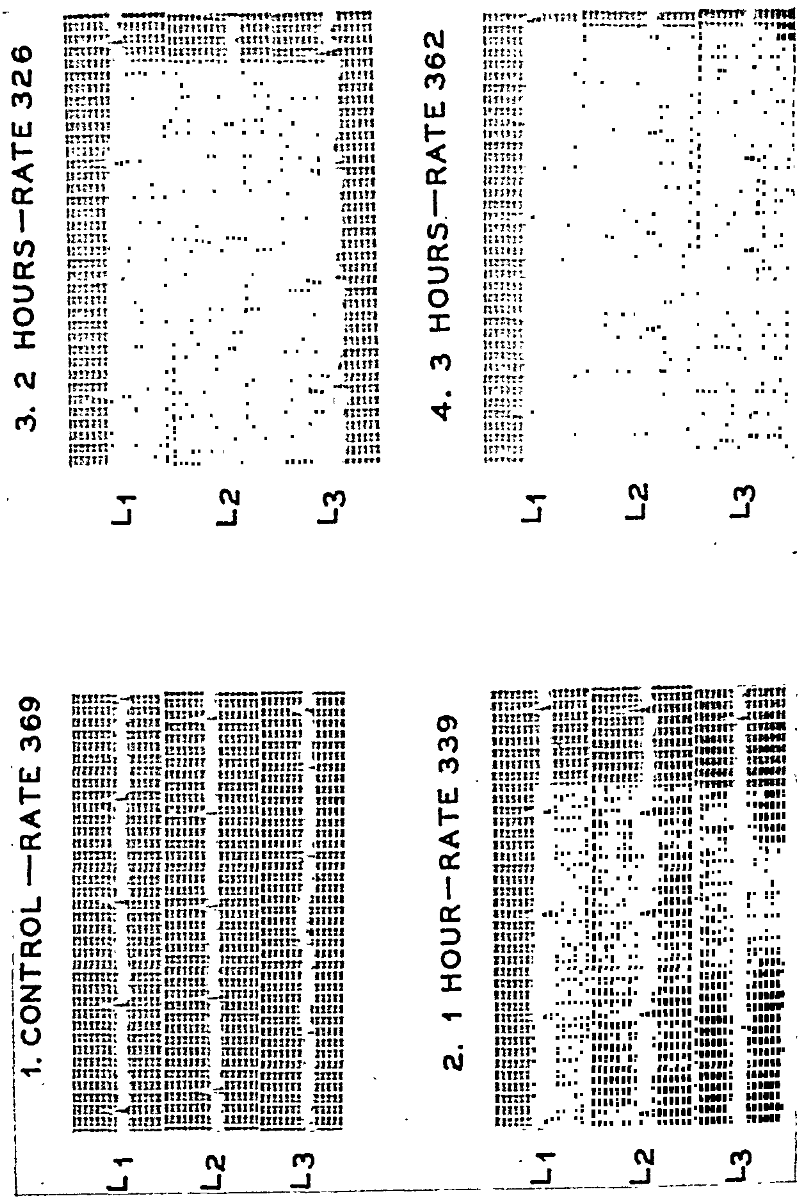

Fig. 3.—Electrocardiograms of a deficient rat before and after the subcutaneous injection of 100 mg. of sodium pyruvate per 100 grams of body weight. The time lines are 1/50 second apart.

Lactic Acid ($CH_3.CHOH.COOH$)

An accumulation of lactic acid in the blood,[4, 16, 17, 18] as well as in the muscle, liver, and heart,[19, 20] of deficient animals is one of the chemical features of vitamin B deficiency. In man, the lack of vitamin B leads to a disturbance in the resynthesis of glycogen from lactic acid.[21] A number of observations have been made on the effect of administering lactic acid or lactate to animals or man. According to Kalaja and Närvanen,[13] lactic acid, when injected subcutaneously in rats in an amount equal to 50 per cent of the lethal dose, decreased the heart rate by about 33 per cent for a period of several hours. The effect on rabbits and pigeons was hardly discernible. Guha[22] found that the ingestion of sodium lactate did not appreciably hasten the appearance of symptoms in rats deficient in vitamin B_1 but that the lethal dose of lactate injected subcutaneously was less for deficient than for normal animals. In Schrader's experiments on rats, lactic acid in the diet did not hasten the onset of symptoms.[11, 23] Lecoq[24, 25] observed that the addition of lactic acid to the diet of pigeons caused them to develop polyneuritis sooner, and prevented the utilization of increased amounts of vitamin B. Hayasaka[26] injected sodium lactate intravenously in man, and observed a higher level of lactic acid in beriberi patients than in normal subjects.

Sodium Lactate, Administrated Orally.—The fatal dose of sodium lactate when given by mouth was not less for deficient rats (over 700 mg.) than for normal rats (500 to 700 mg.) (Table I). The results of giving smaller single doses of lactate by mouth are summarized in Table V. No consistent changes were demonstrated in normal or in deficient rats, although a certain number of changes in the heart rate or in the height of the T waves occurred in both groups after giving lactate. In three cases, T waves became upright or higher.

Three out of four full-grown, normal rats which received daily doses of lactate by mouth for several weeks showed a decrease in weight (16 to 29 grams); two young rats showed a normal increase in weight. No definite changes in the heart rate or electrocardiographic complexes were seen in the control animals (Table III). Two deficient rats received lactate by mouth for eighteen days without a marked decrease in the time required to become deficient (Table IV). The heart rate responded to thiamin, in spite of the administration of lactate.

Sodium Lactate, Administered Subcutaneously.—The fatal dose of sodium lactate, when injected subcutaneously, was not less for deficient rats (over 450 mg.) than for normal rats (350 to 400 mg.) (Table I). The results of giving single, nonfatal doses are recorded in Table V. In control rats the larger doses produced symptoms of weakness and, in two out of eight cases, a decrease in heart rate. In the majority of cases the rate did not change, and no significant changes in the electro-

TABLE V

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF SODIUM LACTATE AND LACTIC ACID

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE* (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE			NUMBER OF RATS AND EFFECT ON T WAVES			REMARKS
				IN-CREASE	NO CHANGE	DE-CREASE	INITIAL FORM OF T WAVES	NO CHANGE	FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	
Sodium Lactate p.o.	Normal	3	250-300	1	2	0	2, T_2 & T_3 upright 1, T_3 flat	1 0	1, T_2 & T_3 higher 1, T_3 upright	
	Deficient	7	200-250	1	5	1 (slight)	4, upright 3, low or flat	3 2	1, low or flat 1, T_1 slightly higher	
Sodium Lactate s.c.	Normal	8	100-200	1	5	2	8, T_2 & T_3 upright 1, low origin	8	Unchanged	
	Deficient	9	100-156	2 (slight)	3	4	2, T_2 & T_3 upright 1, variable 6, low, flat or inverted	1 4	1, T_2 slightly higher 1, flat 2, T_3 upright	Before vitamin B_1
	Deficient after Vitamin B_1	4	125	3 (slight, transient)	1	0	3, upright 1, flat	1 1	1, T_3 slightly lower 1, variable Unchanged	17 to 18 hours after 0.015 mg. vitamin B_1
Sodium Lactate i.v.	Normal	2	100-125	0	0	2	2, upright	2	Unchanged	Ether anesthesia
	Deficient	2	100-150	1 (slight)	1	0	2, low, flat or inverted	0	2, upright or higher	
Lactic Acid p.o.	Normal	6	100-165	0	4	2 (slight)	6, T_2 & T_3 upright 1, T_3 low	5	1, T_1 higher; T_3 diphasic	
	Deficient	4	100-150	1 (transient)	3	0	2, upright 1, T_2 & T_3 slightly high 2, flat	2 2	Unchanged Unchanged	

*In terms of lactic acid.

Vitamin B_1 was given immediately, and seven hours later the heartbeat was still irregular, but the rate had increased to approximately 500. The electrocardiogram later became normal.

Sodium Bicarbonate and Ammonium Chloride

Because of the possibility that the electrocardiographic changes after giving pyruvic or lactic acid, or their salts, were caused by the administration of large amounts of sodium, or by changes in the acid-base balance, control experiments were performed with sodium bicarbonate and ammonium chloride. Barker, Shrader, and Ronzoni[illegible] reported that, in normal human subjects, alkalosis, produced by hyperventilation or by the ingestion of sodium bicarbonate, was accompanied by flattening or inversion of the T waves, whereas acidosis, produced by exercise or by the ingestion of ammonium chloride, was accompanied by an increase in the amplitude of the T waves. Williams, Weiss, and Taylor[illegible] also found

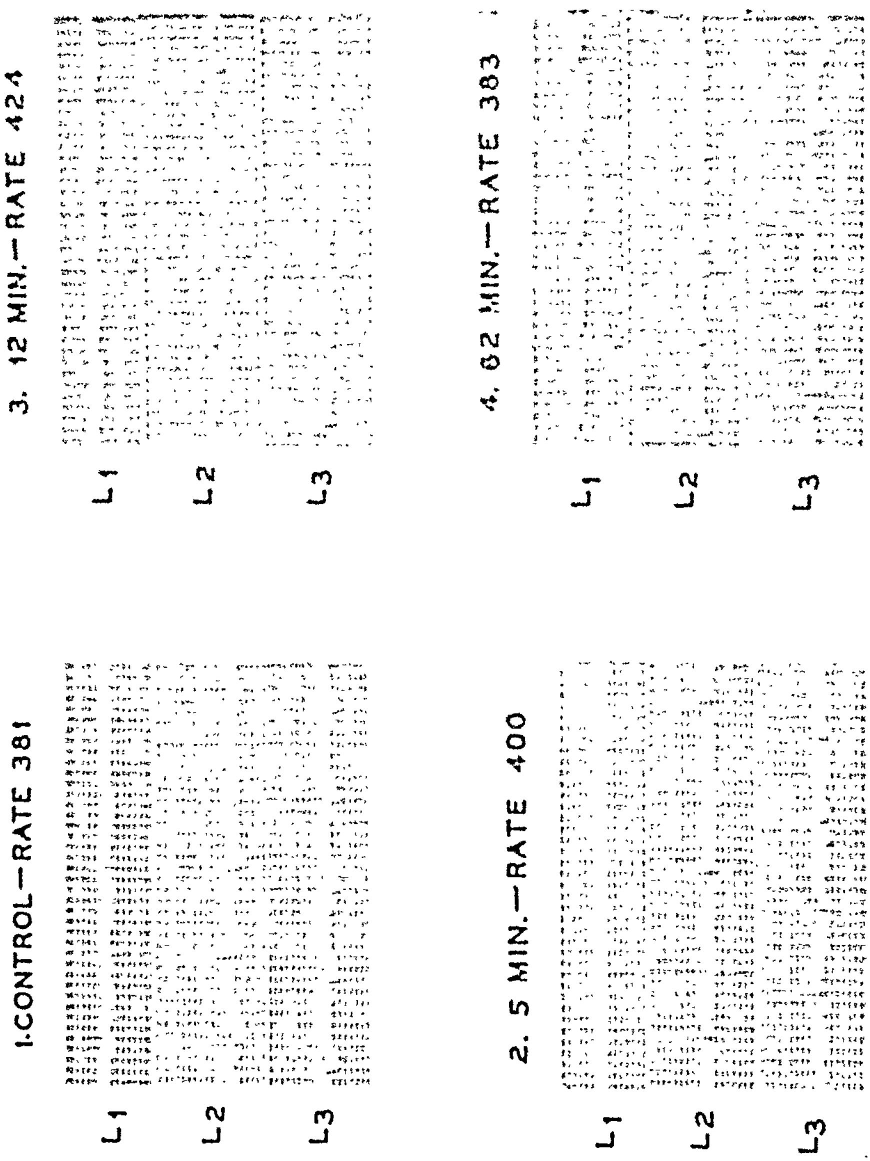

FIG. 1.—Electrocardiograms [illegible]

that the electrocardiographic changes after giving sodium bicarbonate were qualitatively the same as, but usually quantitatively less than, those produced by comparable amounts of sodium pyruvate. Guha[22] observed that ammonium chloride (100 to 222 mg. per 100 grams of body weight) was more toxic than sodium lactate, and apparently equally fatal to normal and vitamin B_1 deficient rats. We used doses of sodium bicarbonate which were comparable in sodium content to 200 mg. doses of sodium pyruvate (calculated as pyruvic acid).

The oral administration of single doses of 180 to 200 mg. of sodium bicarbonate per 100 grams of body weight to two control rats increased the heart rate very slightly in one instance. There was a slight increase in the height of T_1 in one rat, and of T_2 and T_3 in the second animal. In nine experiments deficient rats received from 100 to 200 mg. by mouth, after which the heart rate increased slightly in three instances. In three out of six rats with flat or inverted T waves, T_2 or T_3 became upright or had a slightly higher origin after bicarbonate. After 200 mg. the pH of the urine increased from 6.8 to 9.0, where it remained for at least four hours. The continued administration of sodium bicarbonate by mouth (190 to 270 mg. per day) to three deficient rats for eighteen to twenty-eight days did not change the speed with which they became deficient. The heart rate was unchanged by bicarbonate. In two of the rats, during the first few days of sodium bicarbonate administration, T_2 changed from a flat or inverted wave to an upright one after sodium bicarbonate was given (Fig. 5). The pH of the urine usually increased to 9. It should be noted that sodium bicarbonate had a more marked effect on the acid-base balance than did sodium pyruvate, for doses of 400 mg. of bicarbonate per day rapidly caused tetany in rats, whereas similar doses of pyruvate could be given for an extended period without apparent effect.

The subcutaneous injection of sodium bicarbonate in seven deficient rats and one control rat had no effect on the heart rate. Doses of 115 to 138 mg. of sodium bicarbonate had no definite effect on the electrocardiographic complexes, whereas doses of 200 mg. produced higher T waves in all three of the deficient rats to which they were given. In some of the early experiments the sterile bicarbonate solution was not freshly prepared.

The effect of ammonium chloride (50 to 200 mg.) was studied in six normal and four deficient rats. In normal rats the heart rate was slowed in all but one case, but the T waves were usually not changed. In deficient rats the results on the rate were variable, whereas the T waves were not affected by ammonium chloride.

Methyl Glyoxal ($CH_3.CO.CHO$)

Methyl glyoxal has been found in the blood, urine, and spinal fluid in a few cases of oriental beriberi,[3] as well as in the urine of infants with

various pathologic conditions,[5] including "acute toxic dyspepsia," which may be a manifestation of vitamin B_1 deficiency.[6] Methyl glyoxal has been found in the urine of vitamin B_1 deficient polyneuritic dogs and rats, but in rats it is claimed not to be specific for B_1 avitaminosis.[28] Simola[29] was not able to detect the presence of methyl glyoxal in the urine of rats deficient in vitamin B. Jansen and Westenbrink[30] do not consider it probable that methyl glyoxal intoxication causes polyneuritis. Takamatsu and Sato[31] found that the hearts of rabbits deficient in vitamin B became enlarged after the intravenous and oral administration of methyl glyoxal. The enlargement following the administration of methyl glyoxal was less when vitamin B was given. Ariyama,[32] however, did not observe that intravenous injections had any effect on rabbits, or on the speed with which polyneuritis developed in pigeons.

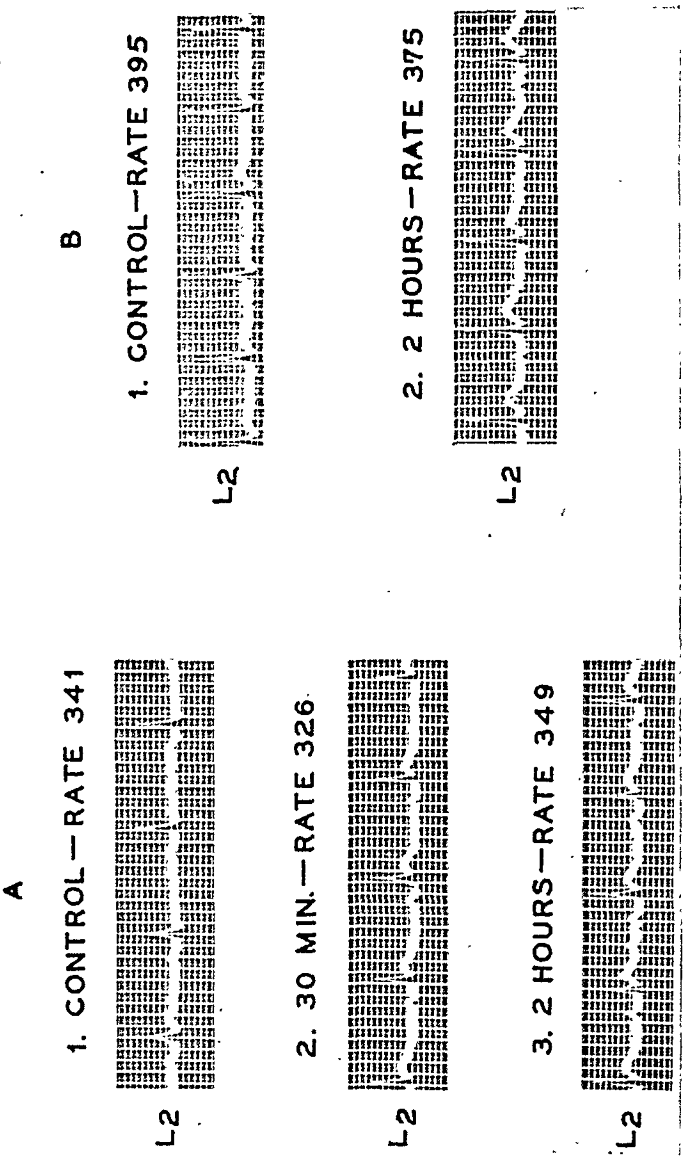

Fig. 5.—Electrocardiograms of two deficient rats before and after the oral administration of 100 mg. of sodium bicarbonate per 100 grams of body weight. The records in *A* were taken before vitamin B_1 was given; those in *B* were taken two days after giving 0.016 mg. of thiamin.

In normal dogs and rabbits, large doses of methyl glyoxal have been found by Martini,[33, 34] and by Goldenberg, Gottdenker, and Rothberger,[35] to act on the vagus center, causing a decrease in heart rate, a fall in blood pressure, and cardiac dilatation. Goldenberg and his co-workers[35] observed changes in the S-T segment, sinus arrhythmia, intramuscular conduction disturbances, and A-V block in the dog's electrocardiogram, as well as a widening of the coronary vessels.

For the experiments to be reported here, solutions of methyl glyoxal were prepared daily from 20 per cent aqueous stock solutions.* The latter were obtained at intervals of several weeks, in order to avoid the possibility of decomposition. The stock solution was a clear, colorless liquid, acid to litmus.

Methyl Glyoxal, Administered Orally.—The fatal dose of methyl glyoxal by mouth was not less for deficient rats (over 200 mg.) than for normal rats (175 to 200 mg.) (Table I). The cardiac changes after single doses of methyl glyoxal (100 to 200 mg.) appear in Table VI. Electrocardiograms were taken on four additional control rats, which received fatal doses of 175 to 300 mg. In normal and in deficient rats no marked changes in the T waves took place for three hours, even after fatal doses; the heart rate decreased somewhat in several cases. It should be noted that Stöhr[36] observed a rise in the liver glycogen within three hours after giving methyl glyoxal by mouth, indicating that it was absorbed during this period.

Three control rats ate less food while receiving daily doses of methyl glyoxal. Two rats lost a small amount of weight, whereas the third lost considerable weight, showed a decrease in heart rate, and died after thirteen days. Daily doses of methyl glyoxal did not affect the electrocardiographic complexes during the period of administration (ten to nineteen days) (Table III). No neurologic manifestations were observed. The sensitivity of control rats to methyl glyoxal is shown by the fact that a fourth rat died after three daily doses of 100 to 150 mg.

While they were receiving repeated doses of methyl glyoxal by mouth, deficient rats responded normally to thiamin (Table IV). Early in the period of administration, three rats were maintained on a given dose of vitamin B_1 for a somewhat shorter time than might have been expected without methyl glyoxal; after longer administration of methyl glyoxal, however, two of the rats appeared to need no thiamin while they were receiving methyl glyoxal. The significance of this is not clear.

Methyl Glyoxal, Administered Subcutaneously.—Methyl glyoxal was found to be absorbed with difficulty from the subcutaneous tissues. Of two normal rats which received 150 and 100 mg., respectively, the first developed marked swelling and was dead the next day, whereas the second had marked swelling for some days, and then developed a slough.

*Prepared by Macmillan and Cleveland, Chemists, Chicago.

TABLE VI

ELECTROCARDIOGRAPHIC CHANGES IN RATS AFTER SINGLE DOSES OF METHYL GLYOXAL AND GLYCERALDEHYDE

	NUTRITIONAL STATE	NO. OF RATS	DOSAGE (MG. PER 100 GRAMS BODY WT.)	EFFECT ON HEART RATE: INCREASE	EFFECT ON HEART RATE: NO CHANGE	EFFECT ON HEART RATE: DECREASE	NUMBER OF RATS AND EFFECT ON T WAVES: INITIAL FORM OF T WAVES	NUMBER OF RATS AND EFFECT ON T WAVES: NO CHANGE	NUMBER OF RATS AND EFFECT ON T WAVES: FORM OF T WAVES AFTER ADMINISTRATION OF SUBSTANCE	REMARKS
Methyl glyoxal p.o.	Normal	3	100-200	0	1	2 (slight)	3, T_2 & T_3 upright	3	Unchanged	
	Deficient	7	107-200	1 (slight)	4	2 (slight)	7, T_2 & T_3 upright	6	1, T_2 & T_3 slightly lower	
Methyl glyoxal i.v.	Normal	2	24-50	0	1	1 (transient)	2, T_2 & T_3 upright	2	Unchanged	Ether anesthesia; rate varies with anesthesia
	Deficient	2	30-42	0	0	2	2, T_2 & T_3 upright	0	2, T_2 & T_3 higher	
Glyceraldehyde p.o.	Normal	3	200-250	0	1	2	3, T_2 & T_3 upright; T_3 low	3	Unchanged	
	Deficient	5	200	0	4	1	2, T_2 & T_3 upright 3, T_2 & T_2 flat	1 2	1, T_2 & T_3 higher 1, T_2 & T_3 higher	T-waves higher with excitement
Glyceraldehyde i.v.	Normal	2	55-75	0	1	1	1, T_2 & T_3 upright 1, T_3 flat or inverted	1 1	Unchanged Unchanged	
	Deficient	2	50	0	2	0	1, upright 1, flat	0 1	1, T_2 & T_3 slightly lower Unchanged	

The only change in the electrocardiograms in the first three hours was an increase in the heart rate in one rat.

Methyl Glyoxal, Administered Intravenously.—Experiments in which methyl glyoxal was injected intravenously are summarized in Table VI. On control rats, records were taken immediately after injection, and, on deficient rats, during and after injection. Normal, as well as deficient, rats may be killed by very small quantities of methyl glyoxal if it is injected rapidly. As the rate of injection was increased until it approached the fatal dose, electrocardiographic changes which are typical in moribund animals appeared, that is, a greatly decreased heart rate and increase in the height of the T wave. The rats recovered rapidly, however, when the injection was stopped. Methyl glyoxal is probably quickly removed from the blood stream by the liver, for Martini[34] found it to be ineffective when injected into the portal circulation. Deficient rats which had received methyl glyoxal recovered satisfactorily after thiamin, and showed no permanent cardiac damage.

The differences in the response of normal and of deficient rats to methyl glyoxal are, therefore, not striking. The fatal dose of methyl glyoxal is small for normal rats. This substance is known to be easily removed from the blood,[34] and changes were seen in the electrocardiograms only during intravenous injection of almost fatal doses.

Glyceraldehyde ($CH_2OH.CHOH.CHO$)

Although glyceraldehyde has not been shown, as far as we know, to be definitely linked with vitamin B_1 deficiency, it was decided to study its effect on deficient rats because it may possibly be an intermediary triose in the breakdown of glucose to lactic acid. Reeves[37] has shown that glyceraldehyde is toxic to the normal rabbit heart, but is efficient in maintaining the rhythmic contractions of the excised amphibian heart. Glyceraldehyde also protects the frog heart against the toxic action of potassium cyanide.[38]

The glyceraldehyde used in the present investigation was a Schering-Kahlbaum product* which was obtained as a powder in 5-gram ampules. With slight heating, it was sufficiently soluble in water to make a 10 per cent solution. A fresh solution was made up for each experiment.

Glyceraldehyde, Administered Orally.—The fatal dose was not determined. Two control rats received 500 and 600 mg., respectively, and two deficient rats received 400 and 600 mg., respectively, without marked symptoms (Table I). The heart rate of the deficient rat which received 400 mg. was decreased forty beats a minute, but the complexes were not significantly affected. After smaller, single doses, few marked changes in the rate or T waves were observed in normal or deficient rats. The heart rate decreased in three out of eight cases (Table VI).

Throughout a period of two to three weeks, young control rats received daily doses of glyceraldehyde by mouth, during which time they

*Obtained from Akatos, Inc., New York.

grew and ate well, although their increase in weight may have been slightly less than that of controls which did not receive glyceraldehyde. The heart rate showed no significant decrease, and the T waves were unchanged (Table III). During the continued administration of glyceraldehyde to deficient rats, the T waves and heart rate responded to thiamin, and the rats appeared to be maintained on a given dose of thiamin as long as when they were not receiving glyceraldehyde (Table IV). One rat was maintained somewhat longer while receiving glyceraldehyde. In order to rule out the possibility that the glyceraldehyde solution was a source of vitamin B_1, two deficient rats were given daily doses of autoclaved glyceraldehyde. During the period of observation (seven to ten days), no apparent difference was observed in the responses of these animals as compared with those which received nonautoclaved glyceraldehyde.

Glyceraldehyde, Administered Subcutaneously.—Glyceraldehyde, like methyl glyoxal, was found to be absorbed with difficulty from the subcutaneous tissues. Two control rats received 300 mg. apiece and were dead within twenty-four hours. One deficient rat and one normal rat received 100 mg. apiece, after which they developed marked swelling, followed by sloughing. The electrocardiograms showed either no change, or a slight decrease in the heart rate and a slight increase in the height of the T waves (two cases).

Glyceraldehyde, Administered Intravenously.—The results are summarized in Table VI. No marked or consistent changes in heart rate or electrocardiographic complexes were observed in the small number of experiments performed.

In summary, the differences in results on normal and on deficient rats after the administration of glyceraldehyde were not striking.

Glucose $(CH_2OH.(CHOH)_4.CHO)$

Numerous observations have been reported on the relation of the vitamin B requirement to the intake of carbohydrate. McCarrison[39] has shown that a high carbohydrate diet hastens the symptoms of deficiency. Lepkovsky, Wood, and Evans[40] found that the glucose tolerance curves of rats were high only when the animals became severely deficient. The observations of Nitzescu and Benetato,[41] and of Kauffman-Cosla, Vasilco, and Oeriu,[42] indicate that there is a decrease in glucose tolerance in B avitaminosis. Guha[22] has discussed the literature, and reported that the vitamin B_1 requirement is independent of the protein-carbohydrate ratio, or the nature of the carbohydrate in the diet. Cowgill[43] points out the importance of the total caloric intake.

It was decided to supplement and control our experiments on intermediary carbohydrate metabolites by cardiac studies after the continued administration of glucose to rats. One series of four deficient rats received glucose subcutaneously (0.67 to 1.80 grams daily) from the twenty-first to the fiftieth day of their first deficiency; another series

of three rats, after a number of previously induced vitamin B_1 deficiencies, received glucose subcutaneously (0.91 to 1.23 grams daily) for fifteen days, then by mouth (1.26 to 1.85 grams) for an additional thirty-three to thirty-five days. The glucose contained no vitamin B_1, as indicated both by the method of Meiklejohn*[44] and by the fact that autoclaved glucose was used during part of the period. Using the heart rate as a criterion, two rats of the first series became deficient for the first time a little sooner (thirty-fourth to thirty-eightieth day on the deficient diet) than control deficient rats (fortieth to forty-sixth day). One rat of the second series also was less able to maintain its body weight after long-continued glucose administration than normal rats. When rats which were receiving glucose became deficient, their heart rates slowed, and the T waves often became flat or inverted, like those of the control deficient rats. The rats quickly recovered a normal rate and had upright, or even high, T waves after thiamin was given. Single doses of glucose had no consistent effect on the heart rate or the height of the complexes, but caused an increase or decrease in one or two cases.

Adenylic Acid

A relation between adenylic acid and the cardiac effects of vitamin B_1 deficiency might be expected, for this acid is involved in muscle metabolism and the oxidation of lactic acid,[45] and also has a definite effect on the heart, causing a decrease in heart rate, impairment of auriculoventricular conduction, and lowering of the blood pressure.[46] Drury, Harris, and Maudsley[47] obtained evidence that the bradycardia of vitamin B_1 deficient rats is not prevented by the injection of barium, as are the bradycardia and heart block produced by adenosine and muscle adenylic acid.[46] More recently, however, Birch and Mapson[48] stated that the bradycardia produced in the rat by certain adenine compounds apparently resembles that of B_1 avitaminosis, and that in both cases the auricular waves disappear at low heart rates. It was also shown by these investigators that rats deficient in vitamin B_1 showed a sensitivity to these compounds, and that their cardiac tissue had a low deaminase activity, which returned to normal after vitamin B_1 was given. Kalaja and Närvanen[13] observed that subcutaneous injections of yeast adenylic acid in rats caused a profound slowing of the heart rate which was not affected by atropinization. The action of adenylic acid was relatively slight in pigeons and rabbits.

Sodium Adenylate, Administered Subcutaneously.—In the present work the fatal dose was not determined, but it is known that adenylic acid and adenosine are relatively nontoxic, and that they are not cumulative in action.[46]

In both control and deficient rats, single doses of sodium adenylate, given subcutaneously, caused no symptoms except a marked, rapid,

*Information on the vitamin B_1 content of the glucose solutions was supplied by Dr. A. P. Meiklejohn.

and transient fall in heart rate. The rate often became very slow, reaching levels seldom seen without adenylate, except when the rats were moribund. Increasing the doses from 5 to 20 mg. was not followed by progressively greater decreases in rate, but 3 mg. gave a smaller and less definite decrease. In most cases the decrease in rate was similar in control and deficient rats, both before and after thiamin (Fig. 6). Two control rats, however, showed only a slight decrease after 10 mg. The difference in dosage and method of injection may account for our failure to obtain the differences between control and deficient rats described by Birch and Mapson.[48] Two deficient rats, which were receiving 10 mg. of sodium adenylate, showed a marked decrease in heart rate even after 4 mg. of atropine. In rats, as in dogs,[46] the decrease in rate is apparently not of vagus origin. The T waves of control rats were unaffected by adenylate. Out of ten experiments on deficient rats, the T waves were somewhat higher in two, and flatter in one, after the various doses of adenylate. Inverted P waves were present in the records of three control and two deficient rats from five to sixty minutes after 5 mg. of adenylate, as well as in several records after larger doses. In a few cases, inverted P waves also appeared in the records of deficient rats which did not receive adenylate. The Q-T interval increased in some instances after giving adenylate.

Single oral or intravenous doses of adenylate or adenylic acid, or repeated daily doses, were not used except in the case of two control rats

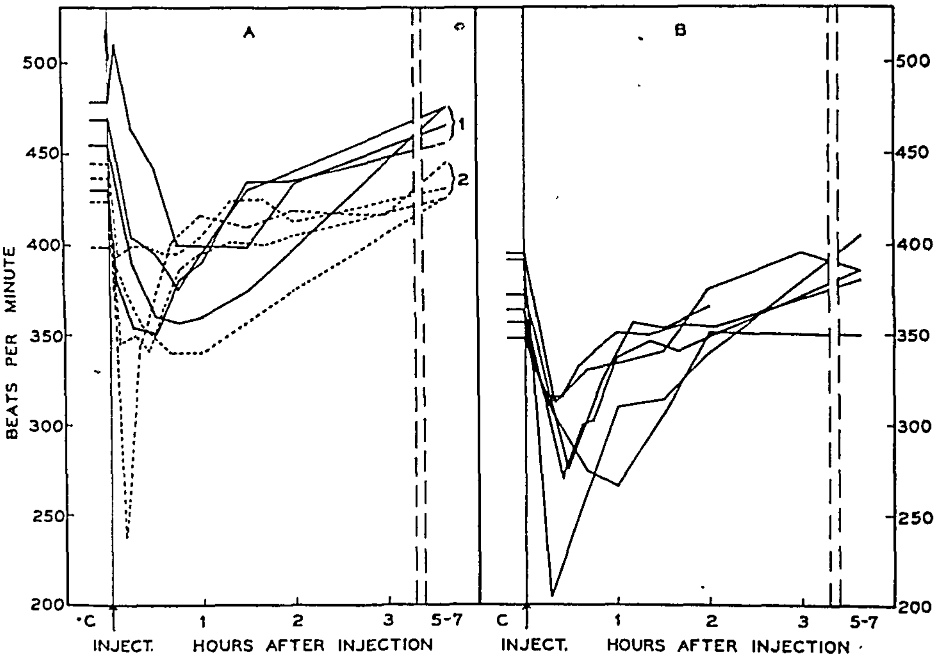

Fig. 6.—Effect on heart rate of the subcutaneous injection of 5 mg. of sodium adenylate per 100 grams of body weight. The average control levels of the heart rates before injection are indicated in column *C*. The graph on the left (*A*) shows the results on (*1*) normal rats and (*2*) rats on a diet deficient in vitamin B_1 which had received thiamin from seventeen to twenty-one hours previously. The graph on the right (*B*) shows the results on rats on a diet deficient in vitamin B_1.

which received large single oral doses of adenylate. These showed moderate slowing of the heart rate, but no change in the electrocardiogram.

Effect of Large Doses of Thiamin on Nondeficient Rats and Dogs

In a previous study[49, 50, 51] on normal persons and on patients with various types of heart disease and edema, we concluded that vitamin B_1 exerts a cardiovascular effect only in the presence of specific deficiency. In view of the work of Tislowitz and Pines[52] on normal dogs, in which they found bradycardia and marked arrhythmia after intravenous injection of thiamin, it is of interest to report here our results with large doses of the vitamin in dogs and rats. After numerous control electrocardiograms, three normal, unanesthetized dogs were followed for periods of four to ten days, during which they received single, daily, intravenous injections of 0.016 to 0.39 mg. of thiamin per 100 grams of body weight, or a total dose of from 2 to 50 mg. per animal. In all cases the heart rate decreased about 40 beats per minute during this period. The dog's heart rate, however, was found to be too variable, both as to the control level and in response to thiamin, to draw any conclusions concerning the decreases in heart rate after thiamin; furthermore, any changes produced were often not reproducible. Short experiments were also performed, in which each dog received from 0.085 to 0.403 mg. of thiamin per 100 grams (10 to 50 mg. per animal) intravenously under chloralose anesthesia. Because of the variations in rate, it was necessary to repeat each experiment with chloralose and saline as a control. In all cases thiamin lowered the rate slightly more than did saline. Two dogs showed marked sinus arrhythmia. The variation in the intervals between beats was often greater at the lower rates, irrespective of whether or not the dog was receiving thiamin.

Single doses of from 0.46 to 2.32 mg. of thiamin per 100 grams of body weight, given subcutaneously, repeatedly exerted no effect on the electrocardiograms of four normal rats; in only one instance was there a decrease in heart rate. Molitor and Sampson[53] found that the heart rate of normal rats was unchanged after intravenous injections of 1.0 mg. of vitamin B_1 per 100 grams. They also report that the lethal dose for rats is 25 mg., thus indicating the enormous difference between therapeutic and lethal doses.

Electrocardiograms on Rats Deficient in Vitamins Other Than Vitamin B_1

During this study we had the opportunity* of recording electrocardiograms on several very young rats which were deficient in vitamins other than vitamin B_1. Four rats with symptoms of riboflavin deficiency had rates of 440 to 550. In one rat the T waves were slightly higher

*We wish to express our appreciation to Dr. Otto A. Bessey for allowing us to take electrocardiograms on his rats.

than those of control rats of the same age. Three of the rats were restudied ten days later, while still deficient in riboflavin, with the same results. One rat which was deficient in vitamin B_6 had a heart rate of 380 and a rather high T_2 and T_3. One older rat, which was deficient in vitamin A, had a normal electrocardiogram and a rate of 510. The lack of vitamin B factors other than vitamin B_1 may produce a slight increase in the height of the T waves, although apparently not the flattening or inversion which may occur in vitamin B_1 deficiency. It is of interest to note that in the present series of rats, which were kept on diets containing yeast which was somewhat less strenuously treated, and thus contained slightly more riboflavin than that previously used,[1] the appearance of high T waves in the first deficiency was more rare; the changes usually consisted of flattening or inversion. With unstandardized leads, Drury, Harris, and Maudsley[47] have previously observed that, in rats, vitamins A and D exert no characteristic influence on heart rate or conduction, nor on the T waves.

DISCUSSION

This study indicates that large doses of the metabolites which were investigated fail to produce, in normal rats, manifestations characteristic of vitamin B_1 deficiency. Deficient rats which received large doses of these compounds usually did not show striking cardiac changes, or develop symptoms of deficiency earlier. The only possible exception was sodium pyruvate. In view of the fact that the amount of pyruvate administered was out of proportion to the concentration present in the body in vitamin B_1 deficiency, it is questionable whether the reduction in the heart rate and changes in the electrocardiographic complexes which were observed in deficient animals have any physiologic significance. In agreement with observations made on normal and deficient human beings,[12] the electrocardiographic changes after the administration of massive doses of sodium pyruvate were not striking. Similarly, nervous symptoms were seldom precipitated by sodium pyruvate. The results reported are in harmony with Peters' view that the acute nervous symptoms of vitamin B_1 deficiency are not caused by any toxic effect of accumulated lactate, or any other metabolite, [8, 54] but a "biochemical lesion" brought about by the "absence of an important factor in the development of energy from carbohydrate." The inability of the cardiac muscle and the central nervous system to obtain energy from normal processes of carbohydrate metabolism in which vitamin B_1 plays a role appears to be more significant than the by-products of such failure.

In considering the mechanism of production of the abnormal T waves which are observed in vitamin B_1 deficiency, it is of interest to note the effects of monoiodoacetic acid.[55] Nahum and Hoff[56] observed in the electrocardiograms of the cat an inversion of the T waves after giving

monoiodoacetic acid, which blocks glycolysis and prevents the accumulation of lactic acid. No change was observed, however, after giving sodium cyanide, which promotes such an accumulation. From this they conclude that changes in the S-T segment in their experiments were related, not to the presence of metabolites or to failure of oxidation, but to a loss of the *anaerobic energy* of glycogen breakdown. Peters and O'Brien[57] have shown that the oxidation of pyruvate which takes place in the pigeon's brain in the presence of vitamin B_1 is inhibited by iodoacetate. These observations suggest that the electrocardiographic changes which we have observed in the rat heart in vitamin B_1 deficiency, which are similar to the changes after administering monoiodoacetic acid, may be brought about by the same mechanism as that suggested by Nahum and Hoff. This is further confirmed by the recent observation that, although the oxygen consumption of the auricles of deficient rats is reduced, there is no significant difference in the oxygen consumption of the ventricular tissue of normal and deficient rats.[58]

SUMMARY AND CONCLUSIONS

1. In order to ascertain whether the cardiac manifestations of vitamin B_1 deficiency could be induced by the presence of intermediary metabolites, electrocardiograms were recorded on rats before and after single and repeated doses of sodium pyruvate, pyruvic acid, sodium lactate, lactic acid, sodium bicarbonate, ammonium chloride, methyl glyoxal, glyceraldehyde, glucose, and sodium adenylate, administered by various routes.

2. The *fatal doses* of sodium pyruvate, but not of pyruvic acid, sodium lactate, lactic acid, methyl glyoxal, or glyceraldehyde, were lower for deficient than for normal rats.

3. In normal rats the heart rate and T waves usually remained unchanged after *single, nonfatal doses* of pyruvate, pyruvic acid, lactate, lactic acid, methyl glyoxal, or glyceraldehyde, when they were administered orally or subcutaneously. The heart rate often decreased after intravenous injection of pyruvate, lactate, or glyceraldehyde. In rats deficient in vitamin B_1, the heart rate often decreased after subcutaneous injection of pyruvate or lactate, or after intravenous administration of methyl glyoxal. In deficient rats the height of the T waves regularly increased after subcutaneous or intravenous administration of sodium pyruvate. In several animals the T waves were also higher after the injection of lactate or sodium bicarbonate. In both normal and deficient rats, sodium adenylate caused no symptoms except a prompt and marked decrease in the heart rate, which was not abolished by atropine. In the majority of cases the P-R interval did not show any definite alteration after the administra-

tion of any of the substances used. Neurologic symptoms corresponding to those in vitamin B_1 deficiency were not observed after nonfatal doses of the metabolites studied.

4. In about one-third of the normal rats, *repeated daily doses* of pyruvate, pyruvic acid, lactate, lactic acid, methyl glyoxal, or glyceraldehyde brought about a slight decrease in the level of the heart rate. The T waves were unchanged, and no neurologic symptoms were induced. In deficient rats which were receiving repeated doses of the same substances, the weight and heart rate usually increased normally after thiamin was given. After administering pyruvate, however, the cardiac response to thiamin was sometimes delayed in deficient rats. In three instances, methyl glyoxal or glyceraldehyde probably lengthened the period during which rats could be maintained on a given dose of thiamin.

5. Large doses of thiamin (0.09 to 2.32 mg. per 100 grams of body weight, corresponding to 60 to 1,600 mg. in a man of 70 kilograms) had little, if any, effect on the heart rate and electrocardiographic complexes of normal rats and dogs, and produced no toxic responses. A vagotonic effect of thiamin on the dog heart could not be definitely established.

6. A few rats which were deficient in riboflavin, vitamin B_6, or vitamin A did not show the T-wave and heart rate changes observed in vitamin B_1 deficiency.

7. The experiments presented indicate that rats deficient in vitamin B_1 were somewhat more sensitive than normal animals to large doses of pyruvate. Because of the size of the doses and the magnitude of the changes, however, no physiologic significance can be attached to the findings. The results of this study indicate that the accumulation of metabolites is probably not an important causal factor in the production of cardiac manifestations in vitamin B_1 deficiency in rats, and support the theory that these manifestations depend on a defect in metabolism, rather than on a toxic effect of circulating metabolites.

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A STUDY OF THE EFFECTS OF NICOTINIC ACID AND RELATED PYRIDINE AND PYRAZINE COMPOUNDS ON THE TEMPERATURE OF THE SKIN OF HUMAN BEINGS

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INTRODUCTION

WHEN it was first reported that nicotinic acid and its amide were of specific value in treating canine blacktongue,[1] there was no information regarding the pharmacologic activity of these pyridine compounds in man. Before these substances could be used in the treatment of pellagra, it was necessary to ascertain whether they were toxic for human beings. Preliminary observations by Spies, Cooper, and Blankenhorn[2] indicated that nicotinic acid could be given safely to normal adults, either orally or parenterally. It was found, however, that when this substance was given orally in large amounts, or was administered rapidly by the parenteral route, a sensation of heat, itching, and tingling, together with flushing of the skin, frequently occurred. This fact, which was noted independently by several investigators,[2] was surprising, for no similar observations had been made on dogs or other experimental animals.[3-6]

Nicotinic acid, when administered orally or parenterally in sufficient doses, produces a characteristic train of symptoms. Within from five to ten minutes after an oral dose of 100 mg., or more, or one or more minutes after the parenteral administration of 10 mg., a sensation of heat occurs in the skin. It usually begins in the face and spreads over the neck, chest, and upper arms. In some cases, the entire body surface becomes involved, although the arms and legs frequently escape, and the surface temperature may actually fall, especially in the lower extremities. The sensation of heat may merge into, or be complicated by, stinging, itching, and tingling of the skin. Occasionally, actual pain is experienced. Simultaneously with this feeling of heat, there is a diffuse flushing of the areas in which the heat is felt. Usually the sensation of heat diminishes before the color returns to normal, and the skin temperature may remain elevated even when the skin feels normal subjectively. These phenomena of vasodilatation are associated with a measurable rise in skin temperature, so that we have available an

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objective gauge of the degree of change occurring in the vessels of the skin. The curve of temperature change may vary from one person to another, but each person repeatedly reacts according to his own pattern. Using rigorously controlled standard conditions in a single subject, it is possible to test drugs of the pyridine series for the presence or absence of vasodilating power. The present paper deals with such a study.

MATERIAL AND METHODS

The subjects of these studies included forty-seven adult men, seven women, and four children. None of them showed evidence of peripheral vascular disease or of local skin lesions. Each test was made when the subject was in the post-absorptive state, i.e., usually after fasting from suppertime until the afternoon of the following day (about twenty hours). Occasionally, subjects fasted only during the period from after breakfast until early afternoon (six hours). For at least one hour, and usually for two hours, before the test, the subject was kept flat in bed in a constant-temperature room (20° C.). Under these conditions, the degree of vasoconstriction became so well stabilized that there was no temperature fluctuation of more than ± 0.3° C. in the region tested for the duration of these tests. In our early studies, all of the subject's clothing was removed, and skin temperature readings were made on the legs, arms, chest, neck, and face. After a few trials, it was found that the most extensive responses to the vasodilators occurred in the face and neck, a point recently stressed by Kunkel, Stead, and Weiss.[7] The data included in this paper are derived from repeated readings of the skin temperature of many areas of the face and neck only.

The temperature measuring unit employed in these studies was the Taylor "Dermatherm,"* which consists of four sensitive thermocouples connected in series to form a thermopile; the terminals are connected to a special millivoltmeter which is calibrated to read in degrees centigrade.[8] Before each series of readings, the thermopile was held on the skin in an area not to be studied, until it was of approximately the same temperature as the skin. Precautions were taken not to press on the skin too hard, as this may alter the circulation in the subjacent region.[9] Before each observation was recorded, the thermopile was held (from four to seven seconds) against the part to be studied, until the oscillation of the recording needle of the millivoltmeter ceased. The time required for completing the fifteen readings was usually two minutes. The time recorded on the charts is that at which the observations were begun.

Fig. 1 shows the fifteen areas on the face and neck where temperature was recorded repeatedly at regular intervals, varying from five to fifteen minutes. After a base line had been established, i.e., when there was no spontaneous temperature change in two or more observations, the substance to be tested was given either orally or intravenously. Skin temperature readings were recorded at regular intervals, until the maximum change was detected and a return toward normal had occurred, or for a sufficiently long period to be sure that no change would appear. Control readings were made a day or two before or after the test, under identical conditions. Whenever a compound was tried for the first time, it was given in much smaller doses and more slowly, and records of skin temperature were not always made.

Since some of the compounds were available in only small amounts, all of the data used in making the charts (Figs. 3, 5, and 7) represent the effect of giving 20 mg. of the test substance intravenously. Each curve in Figs. 3, 5, and 7 is an

*The authors are indebted to Dr. Louis G. Herrmann for his kindness in placing the constant-temperature room and apparatus of the vascular clinic at their disposal, and to Miss Helen Crisenberry for her help in recording the temperature readings.

average of observations on four subjects. In no case was there a considerable variation from the average. The substances studied were: nicotinic acid; its sodium, ammonium, ethyl, and monoethanolamine salts; quinolinic, dinicotinic, 2,6-dimethyl dinicotinic, 6-methyl nicotinic, and isonicotinic acids; nicotinic acid amide; nicotinamide hydrochloride; nicotinic acid N-diethyl amide (coramine); pyridine; 3-amino pyridine; sodium sulfapyridine; vitamin B_6 (2-methyl, 3-hydroxy, 4,5-di-[hydroxymethyl] pyridine); and pyrazine mono- or 2,3-dicarboxylic acids.* The material was dissolved in 20 c.c. of physiologic salt solution or sterile water. The injection was completed within one to three minutes. No untoward reaction occurred with any of the compounds used in this study when they were given in this way.

In an earlier paper, Spies, Bean, and Stone[10] noted a considerable variation after oral administration under the same conditions. Examining only the face and neck, and with other factors rigidly controlled, we later found that the temperature rise in any given case followed a definite pattern when the doses were identical and were administered by the same route. We have repeated intravenous injections and obtained identical responses in one case twice on the same day. The flushing response may be elicited again within an hour after a first reaction when small doses are given parenterally. Although a number of factors, such as intestinal absorption, degree of saturation with nicotinic acid, and rate of excretion, undoubtedly influence the occurrence and severity of the reaction after oral administration to normal persons and pellagrins, these factors made no difference when doses of 20 mg. were given intravenously.

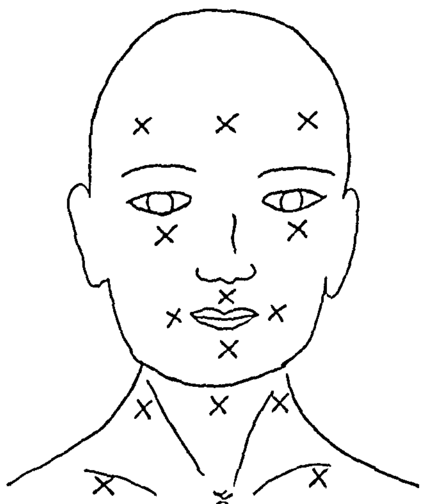


Fig. 1.—Crosses indicate areas on the face and neck where temperature readings were made.

I. PYRIDINE COMPOUNDS WHICH INDUCE THE VASODILATOR RESPONSE

Preliminary reports of the work to be described were made by Spies, Cooper, and Blankenhorn,[2] who noted a reaction characterized by "severe flushing, itching, and tingling, particularly of the face and extremities, which occurred within twenty minutes after the administration of nicotinic acid." Spies, Bean, and Stone[10] more specifically stated that "the giving of nicotinic acid in oral doses of 200 mg., or in intravenous doses of 10 mg. within one minute, nearly always produces dilatation of the small vessels of the face and upper part of the trunk.

*We are indebted to the S. M. A. Corporation, Abbott Laboratories, Merck and Company, and Mead Johnson and Company for the various compounds used in these studies.

This is characterized by increased temperature, flushing, burning, and itching sensations. The pulse, blood pressure, respirations, and electrocardiogram are not regularly changed.''

There was, then, evidence that nicotinic acid produced a vasodilatation in the skin, which was attended by little or no general relaxation of the larger arteries throughout the body. According to the method outlined above, compounds structurally related to nicotinic acid were tested. It was found that identical responses were produced by nicotinic acid (3-pyridine carboxylic acid), sodium nicotinate, ammonium nicotinate,

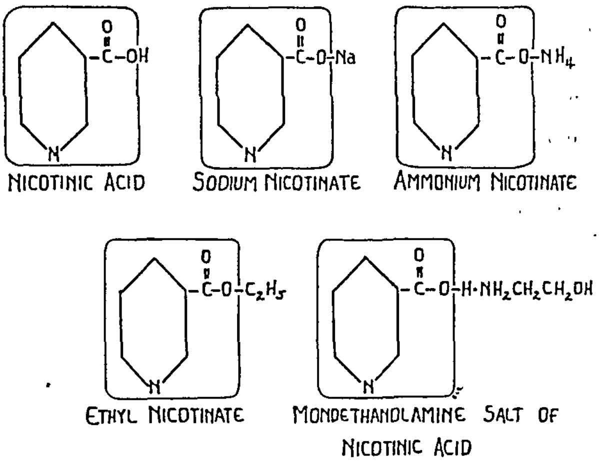


Fig. 2.—Formulas for pyridine compounds which produce temperature rise in the skin The specific radical involved is enclosed in the box.

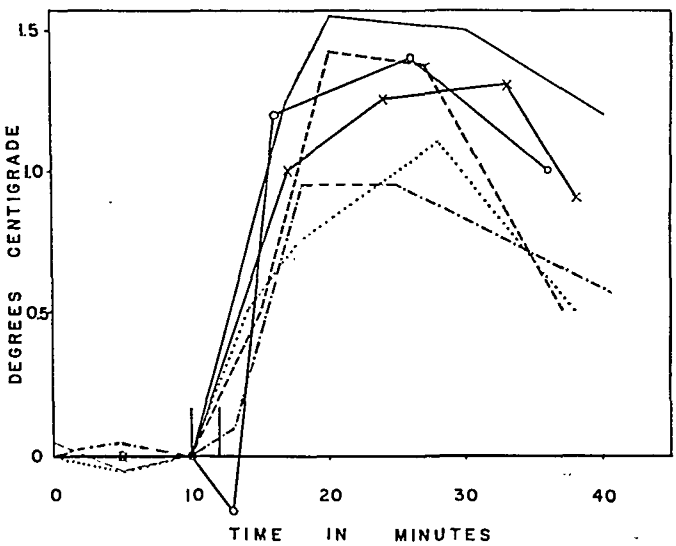
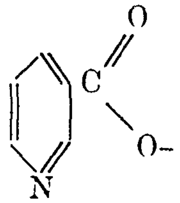
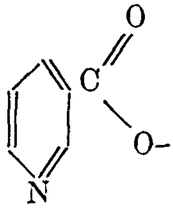


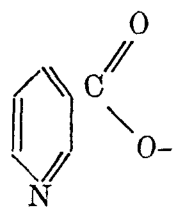
Fig. 3.—Variation in facial temperature after the administration of pyridine compounds. The short vertical lines indicate the period during which the drug was injected. Each record (in Figs. 3, 5, and 7) is an average of tests on four subjects, except for ethyl nicotinate, which was used on only two subjects.

Nicotinic acid	————————————
Sodium nicotinate	———x———x———x———
Ammonium nicotinate	• • • • • • • • • • • • • • • •
Ethyl nicotinate	—•—•—•—•—•—•—•—•—•—
Monoethanolamine salt of nicotinic acid	- - - - - - - - - - - - - - - -
Irradiated nicotinic acid	———o———o———o———

ethyl nicotinate, and the monoethanolamine salt of nicotinic acid (Figs. 2 and 3).* Furthermore, it was found that irradiating nicotinic acid for several hours did not abolish the vasodilator potency of samples from several different sources.† Examination of the structural formulas of these several pyridine compounds reveals that they have in common one radical, namely,  with some atom attached to the unsaturated oxygen atom (Fig. 2). It is believed that the quantitative difference in degree or duration of vasodilatation illustrated in Fig. 1 is an expression of individual differences among subjects. In one subject on whom all of the above drugs were tried, the curves of temperature rise were identical with respect to extent of rise, time of maximum change, and length of time before returning to the base line. There was no essential difference in the reaction produced by any of these compounds.

II. PYRIDINE COMPOUNDS WHICH DO NOT INDUCE THE VASODILATOR RESPONSE

(a.) *Pyridine Compounds Containing the*  *Radical.*—

Similar tests were done with a number of compounds containing the radical which was found to be associated with the flushing reaction, but containing, in addition, other radicals substituted in one or more positions. Dinicotinic acid, 2,6-dimethyl dinicotinic acid, and quinolinic acid produced no flushing or increase in skin temperature (Figs. 4 and 5). In addition to the intravenous administration, large doses (200 to 500 mg.) of these compounds were given orally, with no subjective or objective changes. A dose of 50 mg. of 6-methyl nicotinic acid was given intravenously to one subject, and no increase in temperature occurred, although he reacted readily to 20 mg. of nicotinic acid. The addition of other radicals to the pyridine ring  in the 2, 5, or 6 position, or in all three, caused a loss of the vasodilating property.

*Ferrous nicotinate and quinine nicotinate have been studied recently. Both showed pronounced vasodilator potency, but quinine nicotinate produced extreme tinnitus when given intravenously.

†We are indebted to Dr. C. E. Bills, Research Laboratory, Mead Johnson and Company, Evansville, Ind., for some of these samples, and to Dr. S. P. Vilter, Department of Biochemistry, University of Cincinnati College of Medicine, for others.

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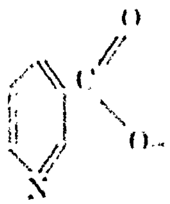
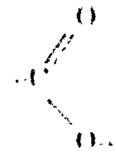
(b.) *Pyridine Compounds Not Containing the*  *Radical.*—

The same procedure was followed with a number of chemicals containing the pyridine ring, but without the  in the 3 position. No increase in skin temperature followed the injection of pyridine, 3-amino pyridine, sodium sulfapyridine, nicotinamide hydrochloride, isonicotinic

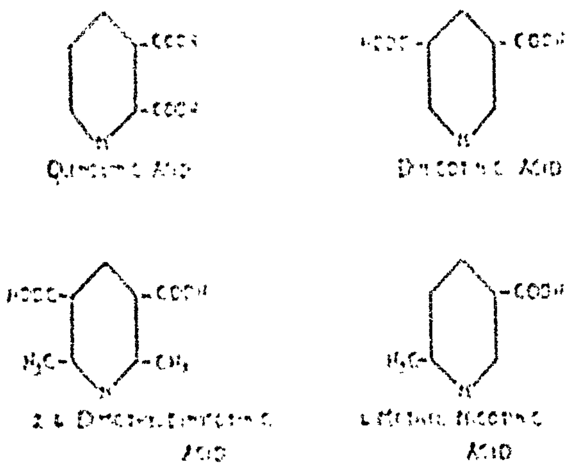
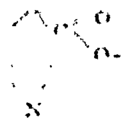


Fig. 4.—Pyridine compounds containing the  O- radical, but without vasodilator potency.

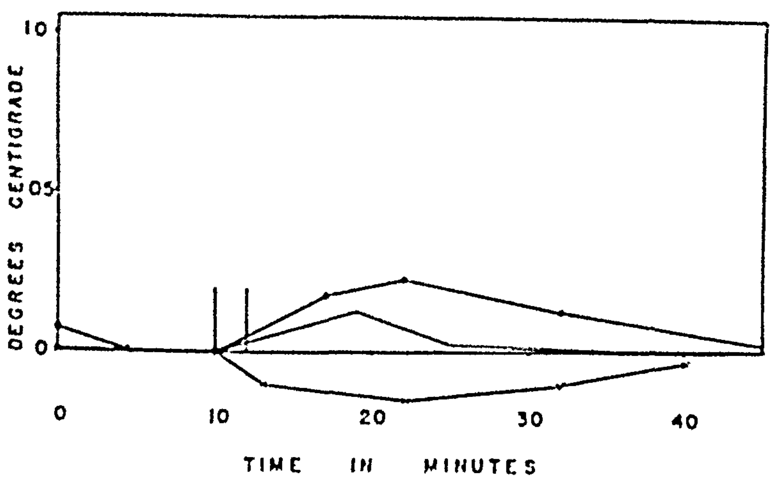


Fig. 5.—Variation in facial temperature after administration of pyridine compounds: Dinicotinic acid, ——x——x——x——; quinolinic acid, ——.——.——.——; 2, 6-dimethyl dinicotinic acid, ————————————. The variations are not considered significant.

acid, nicotinic acid amide, or coramine (nicotinic acid N-diethyl amide) (Figs. 6 and 7). This indicates that pyridine, sulfapyridine, and amino pyridine are not skin vasodilators. Of more interest is the fact that no increase in skin temperature was produced by nicotinic acid amide or nicotinic acid N-diethyl amide. These compounds differ from those producing the temperature rise only in that another radical is substituted for one of the oxygen atoms in the $-\mathrm{C}\genfrac{}{}{0pt}{}{/\!\!/\mathrm{O}}{\backslash\mathrm{O}-}$ group. Vitamin B_6

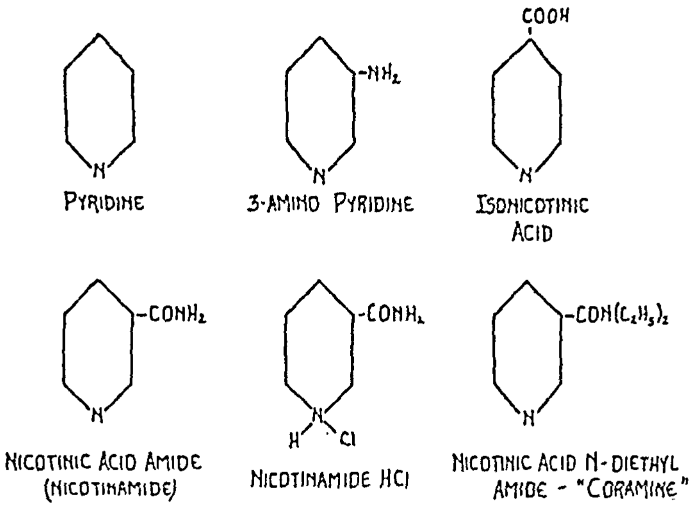
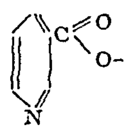


Fig. 6.—Pyridine compounds not containing the  molecule, and without vasodilator potency.

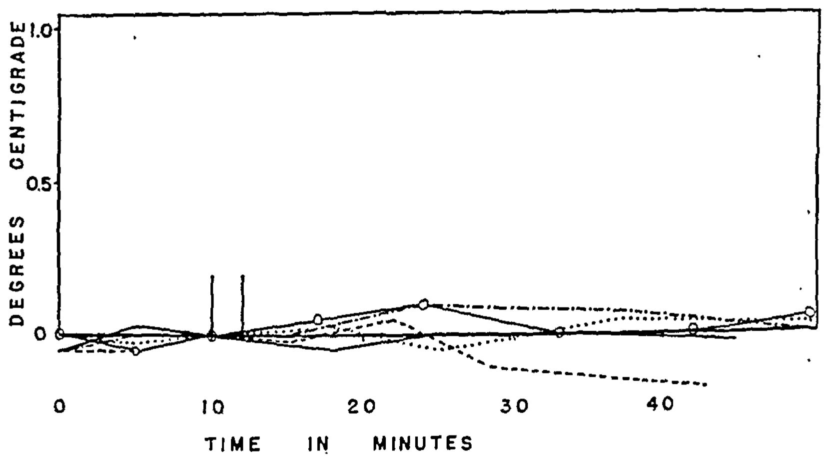


Fig. 7.—Variation in facial temperature after administration of pyridine compounds.

Pyridine
β-amino pyridine
Coramine
Nicotinamide
Nicotinamide HCl

(2-methyl, 3-hydroxy, 4, 5-di-[hydroxymethyl] pyridine) has recently been studied in the same way, and in four normal subjects it was found that there was no temperature response to the injection of 50 mg. intravenously. All subjects tested with the substances which did not evoke the increase in skin temperature were found to respond to nicotinic acid with an increase in skin temperature.

(c.) *Pyrazine Compounds.*—Because there is evidence that both the mono- and 2,3-dicarboxylic acids of pyrazine (Fig. 8) are effective in treating pellagra,[15] we have tested these substances in the same way as the pyridine compounds. In four subjects there was no elevation of skin temperature or any subjective change after the intravenous injection of from 20 to 50 mg. The curves in these cases were flat, as are those in Figs. 3 and 5 and in the control tests.

Subsequently, in a study of the effect of several additional batches of pyrazine monocarboxylic acid on ten subjects, three were observed to flush, and they had a rise of temperature of 0.5° C. These same subjects responded to similar doses of nicotinic acid with a temperature increase of from 1.5 to 2.0° C.

PYRAZINE 2-3 DICARBOXYLIC ACID   PYRAZINE MONOCARBOXYLIC ACID

Fig. 8.—Pyrazine compounds without regular vasodilator potency.

III. ABSORPTION

A comparison of the time which elapsed between the administration of nicotinic acid by intravenous and oral routes and the flushing reaction is presented in Fig. 9. It indicates that the response to intravenous administration began rapidly, reached a peak in about ten minutes, and disappeared rather rapidly. Usually, the temperature had returned to the base line within from thirty to forty-five minutes. The same figure shows that, when 200 mg. were given orally (ten times the intravenous dose in this test) to the same individual, under identical conditions, the temperature rose more gradually, reached the same peak, and then subsided much more slowly. The initial sensations, after intravenous medication is begun, frequently occur during the first minute, while the solution is still being injected, but the end point is not sharp. However, there may be no objective or subjective change for from fifteen to thirty minutes after oral administration.

Another interesting fact in regard to absorption is shown in Fig. 10, in which a comparison of the temperature rise in the fasting and post-

prandial states is made. When 500 mg. were given to the fasting subject, there was a definite rise in fifteen minutes. When the same amount was given after a meal, this rise did not appear for twenty-two minutes. In addition, the peak was 0.7° C. lower than when the material was taken on an empty stomach. Such observations have repeatedly verified the clinical impression[2, 4] that the flushing and burning are less severe when the drug is given orally after meals.

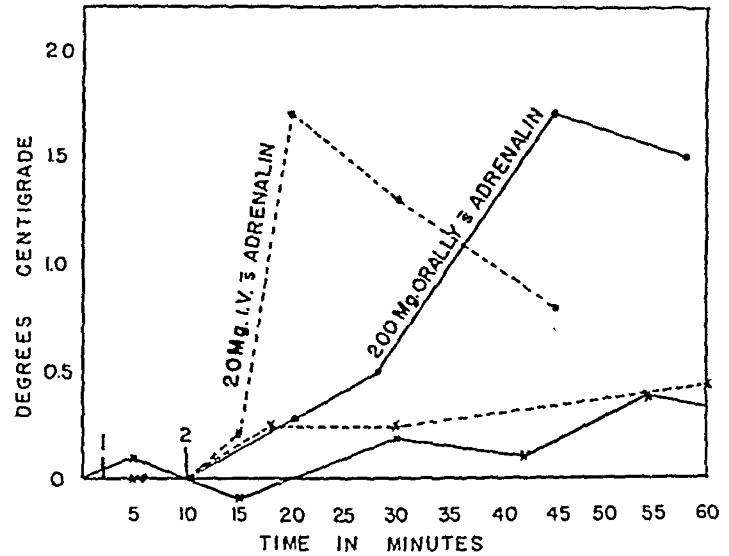


Fig. 9.—A comparison of the temperature response after the oral and intravenous administration of nicotinic acid, with and without previous injection of 1 c.c. of adrenalin. *1*, Time at which 1 c.c. of adrenalin was given intravenously; *2*, time at which 20 mg. of nicotinic acid were given intravenously.

Nicotinic acid intravenously, no previous adrenalin	----.----.----.
Nicotinic acid intravenously, after 1 c.c. of adrenalin	----x----x----x
Nicotinic acid orally, no previous adrenalin	——.——.——.
Nicotinic acid orally, after 1 c.c. of adrenalin	——x——x——x

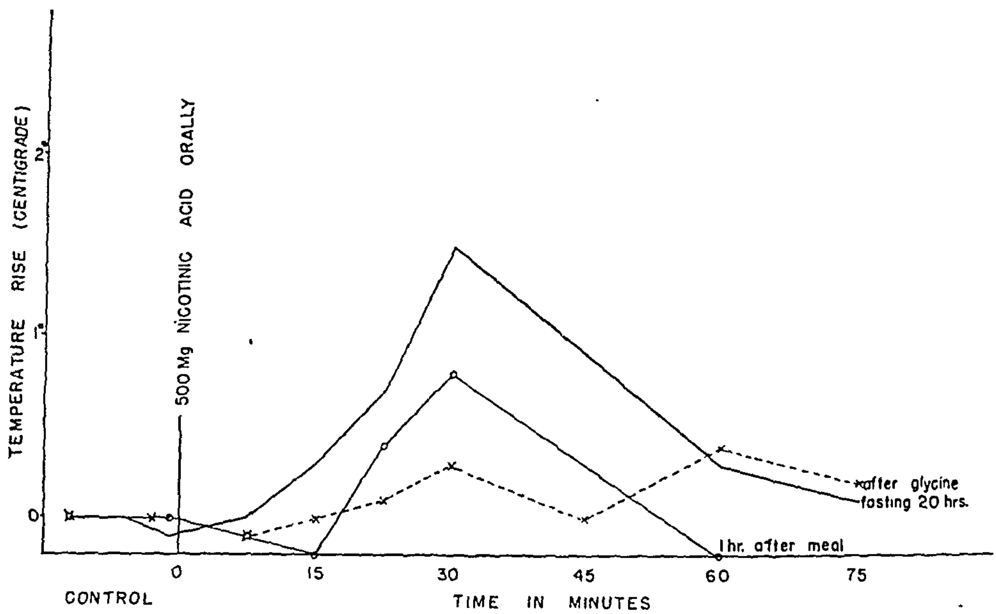


Fig. 10.—A comparison of temperature response to 500 mg. of nicotinic acid, administered orally to a subject in a fasting condition, just after a meal, and after ingestion of 30 Gm. of glycine during the preceding one-half hour.

IV. GLYCINE (AMINOACETIC ACID)

As has been previously reported,[10] we have found that when glycine is given orally in from 30 to 60 Gm. amounts during the one-half-hour period before nicotinic acid is given orally, the vascular response is decreased, or, in many cases, even abolished (Fig. 11). When the same amount of glycine is given orally and nicotinic acid is given by vein (in doses of from 10 to 20 mg.), the flushing response occurs just as it does without glycine.

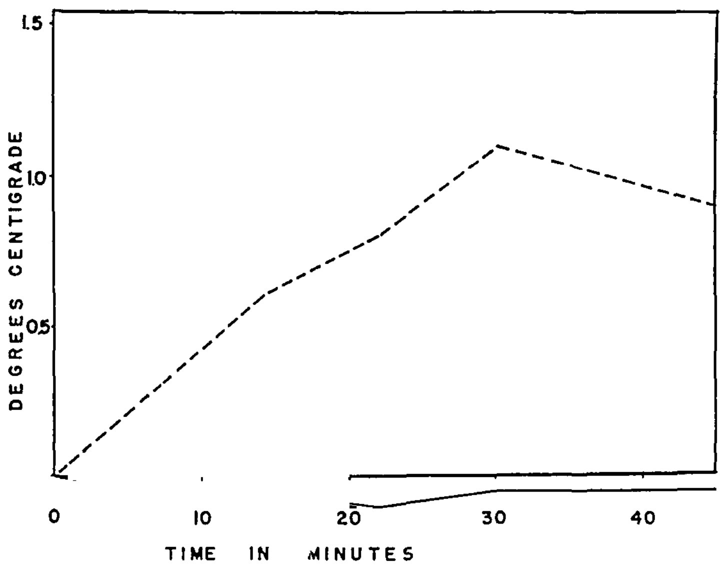


Fig. 11.—A composite graph showing the difference in skin temperature response in ten normal subjects following ingestion of 200 mg. of nicotinic acid after 60 Gm. of glycine were taken orally during the one-half hour before the test (lower line), and without glycine (broken line). In two cases there was a rise of 0.5° C. after glycine, but this was only one-third the rise when no glycine was given in a control test.

V. SITE OF ACTION

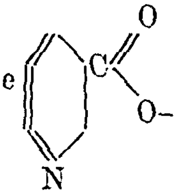
While these studies suggest that a specific radical is essential in producing the temperature rise, they give no indication of the nature of the response. Special studies with adrenalin throw some light on the probable site of the reaction. Fig. 9 shows that when 1 c.c. of adrenalin was given intravenously eight minutes before the administration of nicotinic acid, the vasodilatation was much less than that which took place when no adrenalin was given. In the experiments recorded in Fig. 9, there was no flushing of the face after adrenalin had been given, but there was slight flushing of the neck (with some concomitant rise in surface temperature). A number of studies were carried out in which adrenalin was given after the oral or parenteral administration of nicotinic acid, and it was found that the temperature returned to the base line more rapidly than in control experiments. When adrenalin was injected subcutaneously and allowed to permeate a small area in the skin, this region stood out as a blanched spot in the flushed skin when nicotinic acid, in doses adequate to produce flushing, was

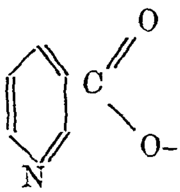
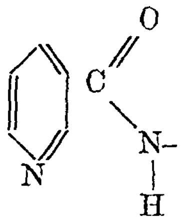
given subsequently. The dosage and timing could be so arranged as to produce no change or only a slight flushing. When very large doses of nicotinic acid and small injections of adrenalin were given, the vasodilator effect would break through, or the adrenalin effect would wear off and the skin become warm. Thus, it is clear that there is an antagonism between adrenalin and nicotinic acid, in so far as the arterioles of the vasolabile regions of the skin are concerned. By inference, we conclude that nicotinic acid acts, directly or indirectly, upon the arterioles in the skin.

We have not been able to obtain any evidence that nicotinic acid exerts a similar effect upon arterioles throughout the entire body, although the evidence to the contrary is not conclusive. We have been able to find no constant and reproducible changes in the electrocardiogram, arterial blood pressure, or pulse rate during the period of flushing. Observations of the mucous membranes in various parts of the body (mouth, nose, rectum, vagina) have not revealed any vascular response during the reaction in the skin. No changes in the retinal vessels could be detected by means of the ophthalmoscope during the dermal reaction. All of these observations lend support to the supposition that the vasodilator action is most active in the skin arterioles.

VI. TOXIC ACTION

We have administered nicotinic acid, or one of the closely related pyridine derivatives, to more than one thousand persons, and have taken it ourselves, with no apparent toxic effect. We have given single doses of 1.5 Gm. orally, 50 mg. intravenously within three minutes, and 75 mg. intramuscularly, to adults, without ill effects, although the flushing lasted longer than with smaller doses. We do not recommend such heroic doses for therapeutic purposes, for it is more pleasant to take repeated small doses, and, in most cases, it is theoretically more sound to give the drug slowly than to flood the organism with a massive amount at one time. In addition to the flushing reaction, which all observers have found in cases in which adequate doses of nicotinic acid were given, a few toxic reactions have been reported. Those who have used the drug extensively have observed an occasional case in which nausea, epigastric distress, or even vomiting has occurred.[10, 11, 14, 15] Throbbing of the head and dizziness have been noted. Rachmilewitz and Glueck[12] observed a case of an "urticarial rash" which lasted for two hours, and Manson-Bahr and Ransford[13] reported that an "urticarial rash appeared on the chest, arms, and front of the thighs. No treatment was given, and within half an hour all symptoms and signs of drug intoxication had disappeared." Alport, Ghalioungui, and Hanna[14] recorded a case in which severe epigastric pain and colic followed each dose of 1 Gm. of nicotinic acid. These all occurred in patients with pellagra. Ruffin and Smith[15] observed lassitude and mental depression, palpitation, cyanosis, substernal oppression, headache, nausea, dyspnea,

derivatives which were studied rarely caused vasodilatation. The vasodilator activity of these pyridine compounds appears to be a specific property which resides only in those which contain the  *structure, free from any substituted or added radicals,* except at the unsaturated oxygen atom.

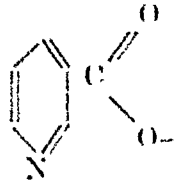
Since satisfactory results have been obtained in treating pellagra with coramine,[10] nicotinamide,[2, 14] and other drugs,[17] it is obvious that the molecule which has a beneficial effect *in the treatment of pellagra* is not necessarily the same as that which produces the vascular reaction. Of the pyridine compounds which we studied, all that produced the changes in the skin vessels are of value in treating pellagra. On the other hand, some of the compounds which do not cause the vascular reaction are potent remedies for pellagra. It is possible, therefore, to get a therapeutic response without the unpleasant flushing. It is also possible, nonetheless, to give nicotinic acid in repeated small doses, so that the skin changes do not occur, in which case it is just as effective. The skin temperature changes produced by nicotinic acid were found to be delayed or aborted by the ingestion of ordinary food just prior to taking the drug. Glycine, by mouth, checks the vasodilatation produced by nicotinic acid. It is possible that glycine interferes with, or inhibits, the absorption of unchanged nicotinic acid, which is therefore not present in a concentration sufficient to arouse the response. It might be crowded out in some such fashion as it is when given after meals during normal digestion. We believe that it is more probable, however, that glycine and nicotinic acid combine to form nicotinuric acid,[1] either in the intestinal tract or in the liver. Nicotinuric acid does not contain the  group; the linkage is , which we have found does not have any observable effect upon the vessels.

It is inferred from studies with adrenalin that the vasodilatation takes place in the arterioles of the skin. Flushing, itching and heat in the skin, and increased motility of the stomach and secretion of gastric HCl are changes similar to those produced by histamine, and it is possible that histamine is liberated by nicotinic acid.

The discovery of a skin vasodilator as innocuous, effective, and cheap as nicotinic acid naturally has suggested many uses for it, in addition to its utility as a vitamin. It has been applied to a great number of skin diseases and may perhaps be of value merely for its local circulatory

effects. The use of nicotinic acid in the treatment of peripheral vascular disease should be discouraged, for, in some cases, it seems to decrease blood flow in the limbs.[10]

SUMMARY AND CONCLUSIONS

1. Of the pyridine compounds which we studied, all which contained the free  radical produced vasodilatation of the skin and an increase in skin temperature in normal human beings, when given intravenously in doses of 20 mg. These compounds were nicotinic acid and its sodium, ammonium, ethyl, and monoethanolamine salts. Pyrazine monocarboxylic acid produced a slight rise of temperature in a few cases. These compounds are all effective in treating pellagra.

2. No vasodilatation followed the administration of similar amounts of quinolinic acid, nicotinic acid amide, nicotinic acid N-diethyl amide, and pyrazine 2,3-dicarboxylic acids, which are effective antipellagric compounds. No vasodilatation followed the injection of similar doses of dinicotinic acid and 2,6-dimethyl dinicotinic acids, which have some antipellagric value.

3. No vasodilatation was produced by 6-methyl nicotinic acid, nicotinamide hydrochloride, and isonicotinic acid. These compounds have not been tested sufficiently for antipellagric potency.

4. No vasodilatation followed the injection of 20 mg. of pyridine, beta-amino pyridine, sodium sulfapyridine, and vitamin B_6 (2-methyl, 3-hydroxy, 4,5-di-[hydroxymethyl] pyridine), which have no specific value in treating pellagra.

5. The use of nicotinic acid in the treatment of peripheral vascular disease should be discouraged, for, in some cases, it seems to decrease blood flow to the extremities, particularly the legs.

6. The site and possible mechanism of the vasodilator action have been discussed.

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A COMPARISON OF THE ORTHODIAGRAM WITH THE TELEOROENTGENOGRAM

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IN A RECENT study of 133 cases in which orthodiagrams and teleoroentgenograms taken at seventy-eight inches were made consecutively, we were impressed by certain marked differences in the heart and chest measurements which were obtained by the two methods of examination. That the cardiac silhouette is magnified in teleoroentgenograms is well known.[1, 2, 3, 4] The magnification of flat objects which occurs in teleoroentgenography can be computed by a simple algebraic equation; the variables are the object-film distance and the target-film distance. The enlargement, however, may be increased by improper centering. Although the fact that the heart shadow is magnified in teleoroentgenograms is well known, the degree of enlargement is not generally appreciated. Furthermore, it is not generally known that the magnification is unequal for the various portions of the heart, and, as a result, that the silhouette is distorted.

A comparison of orthodiagrams and teleoroentgenograms cannot be made with mathematical accuracy because (1) it is impossible to be certain that the chest is in exactly the same position in relation to the film and fluoroscopic screen, (2) it is most difficult to obtain teleoroentgenograms and orthodiagrams in the same phase and degree of respiration (the possibility of error is increased if the teleoroentgenograms and orthodiagrams are not made consecutively), and (3) it is difficult to obtain both in the same phase of the cardiac cycle.

In this study efforts were made to minimize all possible sources of error. The two studies were done consecutively, at the end of an ordinary inspiration, and orthodiagrams were drawn in diastole in order to obtain the largest heart size. Possible errors incident to orthodiagraphy, such as might arise by the use of a large beam of light and movements of the heart during respiration, were well appreciated and avoided.

In order to compare the two methods of examination more accurately, a model of the heart was used. The above-mentioned factors which make impossible an accurate comparison of orthodiagrams and teleoroentgenograms in the living were, therefore, eliminated. Furthermore, the dimensions of the model can be easily ascertained, so that the two methods of roentgenologic examination of the heart can be compared not only with each other, but with actual measurements.

The roentgenographic apparatus used was so arranged that the casette holder and fluoroscopic screen were in different tracks, and could be interchanged by lowering or raising one or the other; the centers of both were in the same vertical

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line. Because of this construction, the film was approximately one inch from the anterior surface of the chest. The necessary correction was made in measuring target-film and object-film distance. The model, made immovable in a box, was placed upon a table, and the center of the anterior surface was made to correspond with that of the fluoroscopic screen. The centers of the screen (and casette), of the model, and of the x-ray tube, at a distance of 6½ feet, were in one line. An orthodiagram was made with the model as close to the screen as possible, and immediately thereafter a film was exposed without moving the model. This procedure was repeated at a distance of zero to six inches, inclusive (actually one to seven inches).

Table I shows the various measurements of the model and those of the orthodiagram and teleoroentgenogram, taken at various distances.

TABLE I

	TRANSVERSE DIAMETER OF HEART (CM.)					AORTA VAQUEZ-BORDET (CM.)				
OBJECT-FILM DISTANCE	ACTUAL MEASUREMENT	ORTH.	PER CENT DIFFERENCE	ROENTGENOGRAM	PER CENT DIFFERENCE	ACTUAL DIAMETER	ORTH.	PER CENT DIFFERENCE	ROENTGENOGRAM	PER CENT DIFFERENCE
1 inch	12.5	12.6	0.8	13.0	4.0	9.2	9.1	-1.1	9.9	7.6
2 inches	12.5	12.6	0.8	13.2	5.6	9.2	9.2	0	10.0	8.7
3 inches	12.5	12.6	0.8	13.3	6.4	9.2	9.0	-2.2	10.1	9.8
4 inches	12.5	12.7	1.6	13.5	8.0	9.2	9.0	-2.2	10.2	10.9
5 inches	12.5	12.5	0	13.6	8.8	9.2	9.0	-2.2	10.5	14.1
6 inches	12.5	12.5	0	13.8	10.4	9.2	9.2	0	10.5	14.1
7 inches	12.5	12.6	0.8	13.8	10.4	9.2	9.1	-1.1	10.7	16.3

Examination of Table I shows that measurements obtained on roentgenograms are consistently higher than actual measurements and those obtained by orthodiagraphy. As the object-film distance increases, the error becomes considerable, and is greatest for the aorta. Although a distance of six or seven inches from film to anterior surface of the heart is not common clinically, this object-film distance may occur in the case of obese individuals, especially women with pendulous breasts, and also when patients have chest deformities, especially pigeon chest. The anteroposterior diameter of the model was 5.6 cm. (2.2 in.), so that, at an object-film distance of six inches from the anterior surface of the heart, the anterior portion of the aorta was 8.2 inches from the film. This distance, although not common, may occur in cases of emphysema, kyphosis, and also when the subject is obese. The orthodiagraphic measurements were but slightly different from those of the model. Although no changes in transverse diameter were noted at distances of six and seven inches, or in the Vaquez-Bordet diameter at five and six inches, this discrepancy may be accounted for by a slight rotation of the model in relationship to the film.

In the 133 cases, teleoroentgenograms were made immediately after the orthodiagrams. A point slightly to the left of the center of the chest, midway between the most caudal portion of the aorta and lowermost portion of the heart, was marked upon the fluoroscopic screen, and the tube, 6½ feet distant, was centered to this mark. Films were exposed at the end of a normal inspiration.

A comparison of the measurements obtained on orthodiagrams and teleoroentgenograms reveals that, in nearly all cases, the heart and

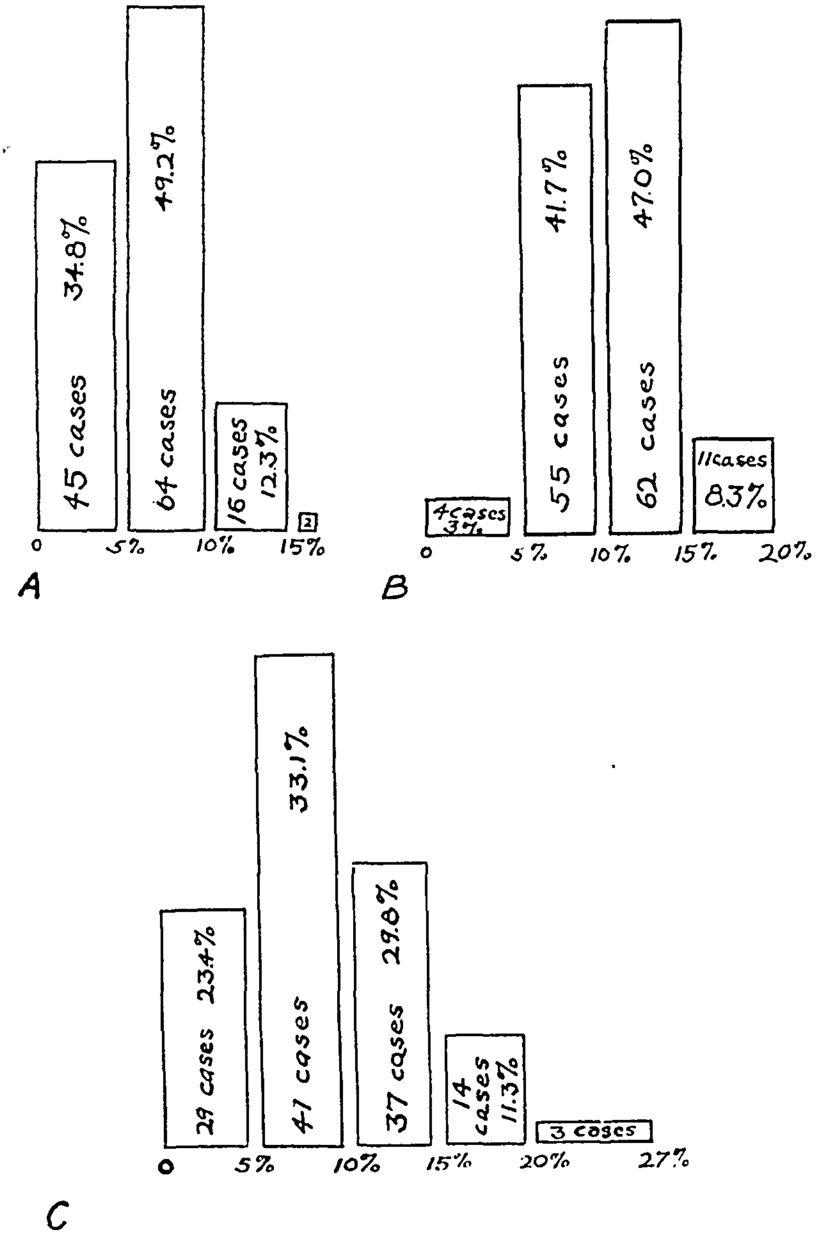

Fig. 1.—*A*, Percentage magnification of transverse diameter of cardiac silhouette in teleoroentgenograms compared with that in orthodiagrams. *B*, Percentage magnification of transverse diameter of chest in teleoroentgenograms compared with that in orthodiagrams. *C*, Percentage magnification of Vaquez-Bordet diameter of aorta in teleoroentgenograms compared with that in orthodiagrams.

chest appear larger in the teleoroentgenograms than in the orthodiagrams. The transverse diameter of the heart was measured satisfactorily in 130 cases, and averaged 6.6 per cent larger in the teleoroentgenogram than in the orthodiagram; the magnification varied from 0 to 16 per cent (Figs. 1*A* and 2). *Andrew and Warren,*[1] *in their* study of distortion in roentgenograms, calculated that the magnification of the heart was 6 per cent at a target distance of six feet. In three cases (2.3 per cent), the diameters were equal, in forty-five cases (34.8 per cent) the diameter was 1 per cent to 5 per cent larger; sixty-four diameters (49.2 per cent) were 6 per cent to 10 per cent larger, and eighteen (13.8 per cent) were between 11 per cent and 16 per cent larger. It must be emphasized that the transverse diameter of most hearts is influenced by the height of the diaphragm. The observed difference, therefore, may be inaccurate, because the height of the diaphragm may not have been the same in all cases; in general, however, it is apparent that the transverse diameter of the heart is larger in the teleoroentgenogram than in the orthodiagram. The average variation is approximately that obtained with the model at an object-film distance of three inches.

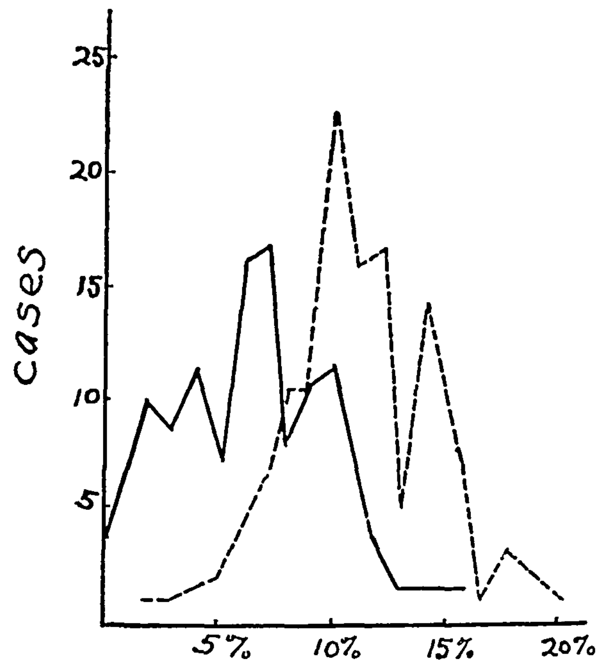

Fig. 2.—Comparison of magnification of transverse diameter of heart (solid line) and chest (dotted line).

The transverse diameter of the chest was measured satisfactorily in 132 cases, and averaged 11.1 per cent higher in the teleoroentgenogram than in the orthodiagram (Figs. 1*B* and 2). As in the case of the cardiac silhouette, an error may arise because of differences in the phase or degree of respiration. Another factor which may be the cause of considerable error, and is frequently not appreciated, is the depth

and shape of the chest. The further the greatest transverse diameter of the chest is from the film, the greater the magnification; if the chest is irregular, the magnification will be unequal (Fig. 3). This factor may be responsible for the greater percentage increase in the transverse diameter of the chest as compared with that of the heart.

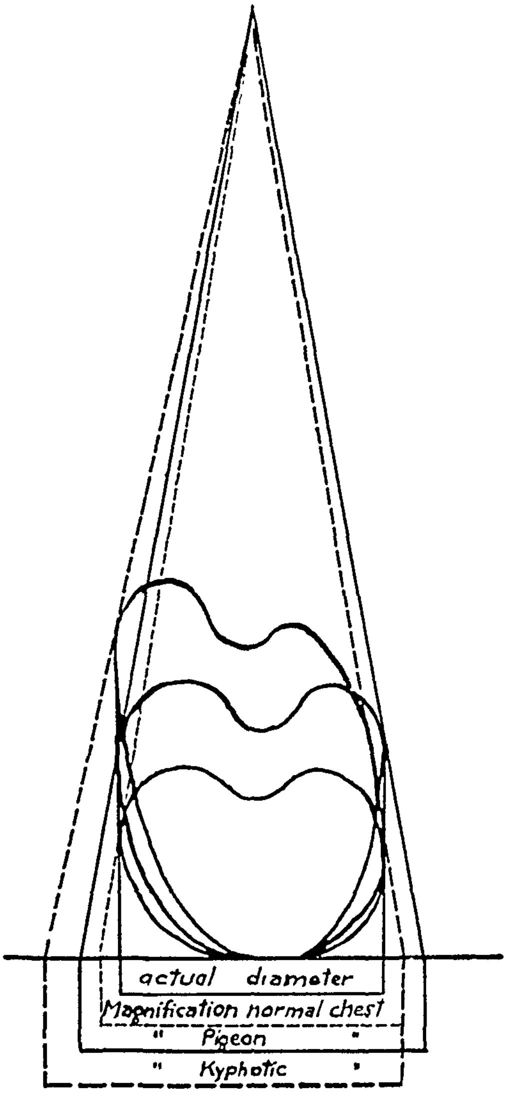

Fig. 3.—Effect of shape of chest upon distortion and magnification.

In four (3 per cent) cases, the transverse diameter of the chest in the teleoroentgenogram was 2 per cent to 5 per cent greater than in the orthodiagram, in fifty-five cases (41.7 per cent), 6 per cent to 10 per cent larger, in sixty-two cases (47 per cent), 11 per cent to 15 per cent larger, and in eleven cases (8.3 per cent), 16 per cent to 20 per cent larger. In 118 cases, the enlargement varied from 7 per cent to 16 per cent.

Inasmuch as the percentage increase in the transverse diameter of the chest is greater than that of the heart in teleoroentgenograms, it follows

that the cardiothoracic ratio should be less in teleoroentgenograms than in orthodiagrams. This was computed in 129 cases. The cardiothoracic ratio was not computed in four cases, because the transverse diameter of the chest, or of the heart, or both, could not be measured. In nineteen (14.7 per cent), the cardiothoracic ratio was the same by both methods. In twenty-five (19.4 per cent), the cardiothoracic ratio in the orthodiagram was .01 larger, in twenty (15.5 per cent), .02 larger, in twenty-four (18.6 per cent), .03 larger, in eighteen (14.8 per cent), .04 larger, in twelve (9.3 per cent), .05 larger, and in eleven (8.5 per cent), varied from .06 to .09 larger (Fig. 4). In ninety-six (74.4 per cent), the cardiothoracic ratio in the orthodiagram was .01 to .05 larger than in the teleoroentgenogram.

The diameter of the aorta was compared in 124 cases (Fig. 1*C*). In only five cases (4 per cent) was the Vaquez-Bordet diameter the same in the orthodiagram and teleoroentgenogram; in all others the latter showed a larger diameter, and the enlargement varied from 2 per cent to 27 per cent. In seventy-eight (62.9 per cent), the enlargement was between 6 per cent and 15 per cent, and, in fourteen (11.3 per cent), the enlargement varied from 16 per cent to 20 per cent. In three (2.4 per cent), the enlargement was over 20 per cent. In any given subject, the object-film distance of the descending aorta in the posteroanterior view is greater than that of other parts of the heart, including the ascending aorta; it is to be expected, therefore, that the greatest magnification would occur here.

DISCUSSION

Examination of Tables I and II shows that magnification of the size of the heart in teleoroentgenograms is considerable; even at a distance of 6½ feet the error is sufficiently great to cause considerable magnification. With proper centering, magnification is dependent upon target-film and object-film distances. The error incident to these factors can be computed for a flat object by the following formula: Error (X) is to the actual size of object as the object-film distance is to the target-object distance. Using the measurements in Fig. 5, the error (X) is determined by the following equation:

$$X : 12 :: 5 : 67$$
$$X = .9$$

The magnification, therefore, is 7.5 per cent. It is apparent that the less the target-film distance, the object-film distance remaining the same, the greater the magnification. Conversely, the less the object-film distance, the target-film distance remaining the same, the less the magnification. If the above distances remain the same, the larger the object, the greater the actual error (X); the percentage difference, however, remains the same.

When dealing with an asymmetrical object such as the heart, the object-film distance will vary slightly for different portions. According to Roesler,[2] the distance of the left lower pole of the heart from the front of the chest averages 3 to 4.5 cm.; that of the right border averages 4 to 6 cm., that of the ascending aorta, 5 to 7 cm., and that of the pulmonary artery, 5 cm. The enlargement of the cardiac silhouette is therefore unequally distributed, and as a result, the silhouette is distorted (Fig. 6*A*). Distortion of a normal heart in a normal chest is admittedly slight, but in the obese or in patients with chest deformities this may be accentuated. In Fig. 6*B*, tracings of teleoroentgenograms of a model, taken at different object-film distances, are superimposed; the degree of magnification is unequally distributed, and, consequently, the shape of the heart is slightly altered. There was no additional error caused by improper centering, for the target was centered upon the center of the model; clinically, if the target is centered upon the center of the chest, the distortion of the cardiac silhouette may be increased.

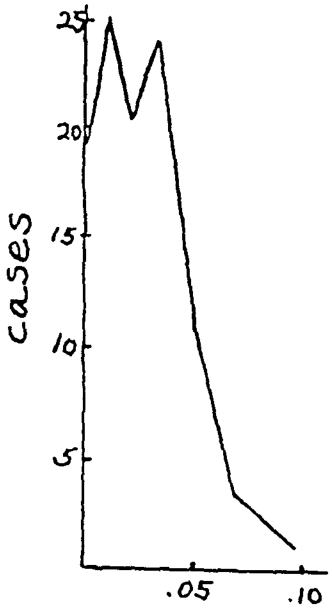

Fig. 4.

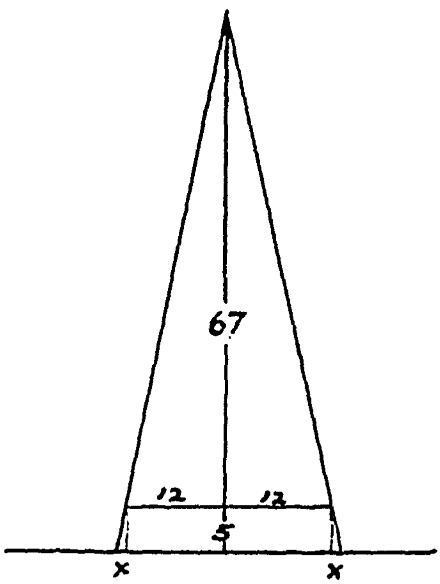

Fig. 5.

Fig. 4.—Magnification of cardiothoracic ratios obtained from orthodiagrams compared with those from teleoroentgenograms.

When the shape of the chest is normal, its greatest, or projected, diameter is considerably more posterior than the greatest, or projected, diameter of the heart. The distance from the plane of the greatest diameter of the bony thorax to the front of the bony thorax at the level of the nipple was measured in fifteen cadavers, and varied from 7 to 11.7 cm. In the living, the distance (object-film distance) of the projected diameter is further increased by the thickness of the overlying tissues. It is therefore apparent that, in roentgenograms, the percentage magnification of the chest is greater than that of the heart, because the object-film distance of the projected diameter is greater (Fig. 2). In

deformed, or in deep, chests, in which the object-film distance of the greatest diameter is unusually large, the magnification will be increased, and, in the former, the enlargement may be unequal, and, consequently, the silhouette will be distorted (Fig. 3).

Inasmuch as the degree of magnification of the chest is greater than that of the heart in teleoroentgenograms, the cardiothoracic ratio obtained by the latter method of examination is usually smaller than that obtained by orthodiagraphy (Fig. 4). In teleoroentgenograms, the cardiothoracic ratio is not only dependent upon the diameter of the heart and chest, but also upon the distance of the projected diameters from the film. In deep chests, or in deformed chests, in which the projected diameter of the chest is more posterior than normal, the increased magnification of the chest as the result of this factor may be considerable and may more than counterbalance the effect of slight magnification of the heart upon the cardiothoracic ratio. In these chests, therefore, the cardiothoracic ratio may be within normal limits when the heart is actually enlarged. The importance of the object-film distance of the projected diameters of the heart and chest can be illustrated by comparing anteroposterior views with posteroanterior views. In Fig. 6C, the teleoroentgenograms (anteroposterior and posteroanterior views) of a man, aged 48, who was suffering from syphilitic aortitis, are superimposed. The films were exposed consecutively at a distance of seventy-eight inches; the chest was of average depth. The transverse diameters of the chest and heart vary considerably; the heart appears larger in the anteroposterior view, and the chest appears larger in the posteroanterior. As a result, the cardiothoracic ratio is .61 in the anteroposterior view, and .51 in the posteroanterior view. It is clear, therefore, that, in teleoroentgenograms, the cardiothoracic ratio is not only dependent upon the diameter of the heart and chest, but is also influenced by the shape of the chest. In orthodiagrams the latter factor is not operative.

In addition to differences resulting from unequal magnification of the heart and chest, the cardiothoracic ratio is also influenced by respiration, and by the position of the chest in relationship to the fluoroscopic screen or film. The phase of respiration is of particular importance. During inspiration, the transverse diameter of the chest increases, the heart usually assumes a more vertical position because of the descent of the diaphragm, and, as a result, the transverse diameter of the heart is decreased, with a consequent decrease in cardiothoracic ratio. Conversely, during expiration, the transverse diameter of the chest decreases, the heart assumes a more horizontal position and its transverse diameter is increased, and the cardiothoracic ratio is therefore larger. It is, therefore, obvious that cardiothoracic ratios obtained from teleoroentgenographic measurements are not only influenced by divergent rays, but also by the phase

of respiration. The effect of the phase of the cardiac cycle and position of the chest is apparent, and requires no further explanation.

Comparison of the measurements obtained in 133 cases with those of the model shows that in teleoroentgenograms the greatest magnification is of the aorta. Table II shows measurements obtained from roentgenograms of the model at varying target-film and object-film distances. Although the error at a distance of 6½ feet is considerable, especially with increased object-film distances, at sixty and forty-eight inches, provided the object-film distance remains the same, the magnification is considerably greater. The aorta is magnified most, but this is obvious because the descending aorta is farthest from the film. The greater

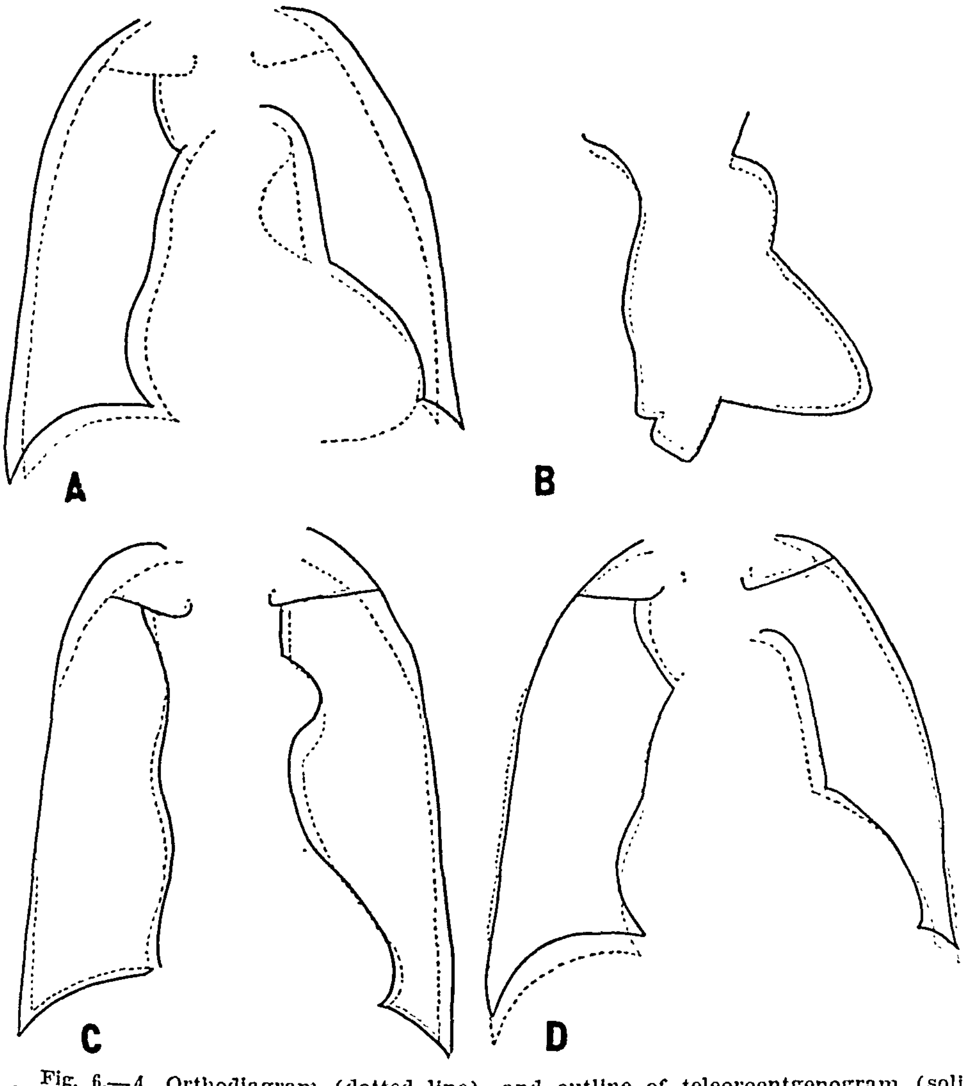

Fig. 6.—*A*, Orthodiagram (dotted line), and outline of teleoroentgenogram (solid line), taken at seventy-eight inches, of patient with hypertension and arteriosclerosis, superimposed. The two were made consecutively. *B*, Outlines of teleoroentgenograms of model of heart, taken at an object-film distance of two inches (dotted line) and five inches (solid line), superimposed. *C*, Outlines of teleoroentgenograms taken at seventy-eight inches, of patient suffering from syphilitic aortitis, superimposed; solid line is posteroanterior view, dotted line is anteroposterior view. The two were made consecutively. *D*, Outlines of teleoroentgenograms taken at seventy-eight inches of same patient as in Fig. 6*A*, superimposed. Solid line is postero-anterior view; dotted line is anteroposterior view.

magnification of the aorta, as compared with the heart, is therefore primarily the result of greater magnification of the descending aorta. In the model, the descending aorta was only 2.2 inches from the anterior surface of the heart. Clinically, therefore, the elongated, uncoiled aorta in an emphysematous or kyphotic chest should be even more magnified, because in these cases the depth of the chest and, therefore, the distance of the descending aorta from the front of the chest are greatly increased. It has been shown that even in severe kyphoscoliosis, regardless of the position of the heart in relation to the spine, the descending aorta closely follows the spine.

Inasmuch as the object-film distance in the posteroanterior view is greater for the descending aorta than for the ascending aorta, it is obvious that, in teleoroentgenograms, not only is the aorta magnified, but the magnification is unequal. The "uncoiled" aorta in Fig. 6*D* appears to be wider in the posteroanterior view than in the antero-posterior, and the significant changes are confined to the descending aorta. Inasmuch as the target-film distance of the chest as a whole was not changed, and the position of the chest in relation to the film was approximately the same, the change in the diameter of the aorta in this case can be caused only by a change in the object-film distance of the descending aorta; the latter is smaller in the anteroposterior view. The converse occurs in the case of syphilitic aortitis (Fig. 6*C*), with dilatation of the ascending and transverse portions of the aortic arch. The distortion of the aorta is greatest in the anteroposterior view, probably because the object-film distance of the involved portions of the aorta is greater in this view.

In carefully drawn orthodiagrams, the factors causing distortion are not operative because the target is not stationary and parallel rays are

TABLE II

TRANSVERSE DIAMETER (CM).

OBJECT-FILM DISTANCE OF HEART	ACTUAL MEASUREMENT	TARGET-FILM DISTANCE			PER CENT DIFFERENCE		
		78″	60″	48″	78″	60″	48″
2 inches	12.5	13.2	13.4	13.5	5.6	7.2	8.0
3 inches	12.5	13.4	13.6	14.0	7.2	8.8	12.0
4 inches	12.5	13.6	13.9	14.3	8.8	11.2	14.4
5 inches	12.5			14.8			18.2
6 inches	12.5			15.0			20.0

AORTA VAQUEZ-BORDET (CM.)

OBJECT-FILM DISTANCE OF AORTA	ACTUAL MEASUREMENT	TARGET-FILM DISTANCE			PER CENT DIFFERENCE		
		78″	60″	48″	78″	60″	48″
4.2 inches	9.0	9.7	9.8	10.1	7.8	8.9	12.2
5.2 inches	9.0	9.9	10.1	10.3	10.0	12.2	14.4
6.2 inches	9.0	10.0	10.4	10.7	11.1	15.6	18.9
7.2 inches	9.0			10.8			20.0
8.2 inches	9.0			11.1			23.3

used. Although great difference of opinion exists as to the relative merits of the two methods of examination, most authorities agree that measurements obtained by careful orthodiagraphy are more accurate than those by teleoroentgenography. Although, as stated above, it is not possible to compare orthodiagrams and teleoroentgenograms with any degree of accuracy because of the factors which may cause distortion and magnification, measurements obtained by the two methods of examination of the model of the heart, in which these factors are eliminated, indicate that orthodiagrams, when properly done, are more accurate than teleoroentgenograms. However, if teleoroentgenograms are made at a distance of not less than 72 inches, and if the subject is neither obese nor has a thick or deformed chest, the differences in measurement are usually not great enough to be of clinical importance.

SUMMARY AND CONCLUSIONS

1. Measurements of orthodiagrams were compared with those of teleoroentgenograms, taken at a distance of seventy-eight inches, in 133 consecutive cases. In each instance, the teleoroentgenogram was taken immediately after the orthodiagram had been made.

2. In 130 cases, the transverse diameter of the heart averaged 6.6 per cent larger in the teleoroentgenograms, with a range from 0 to 16 per cent. The comparison may not be accurate because (1) the position of the chest, (2) the phase and depth of respiration, and (3) the phase of the cardiac cycle may have varied in the two methods of examination.

3. The transverse diameter of a model of the heart was considerably magnified in the teleoroentgenograms. At a target-film distance of seventy-eight inches and an object-film distance of two inches, the magnification was 5.6 per cent; at three inches, 7.2 per cent; and at four inches, 8.8 per cent. The magnification increased with a decrease in the target-film distance; at forty-eight inches, with an object-film distance of four inches, it was 14.4 per cent.

4. The transverse diameter of the chest averaged 11.1 per cent larger in teleoroentgenograms, with a range from 2 to 20 per cent.

5. The cardiothoracic ratio was usually smaller in the teleoroentgenograms than in the orthodiagrams. In 110 of 129 cases, the cardiothoracic ratio was .01 to .09 greater in the orthodiagrams; in nineteen, the cardiothoracic ratio was the same as that in the teleoroentgenograms.

6. In 119 of 124 cases, the Vaquez-Bordet diameter of the aorta was larger in the teleoroentgenograms, varying from 2 to 27 per cent; in seventy-eight (62.9 per cent), the magnification varied from 6 to 15 per cent. In fourteen (11.3 per cent), the magnification varied from 6 to 20 per cent. In five cases (4 per cent) the diameters were the same.

7. At a target-film distance of seventy-eight inches, with the model of the heart two inches from the film (aorta, 4.2 inches), the increase in

the Vaquez-Bordet diameter was 7.8 per cent; at four inches (aorta, 6.2 inches), it was 11.1 per cent. At a target-film distance of forty-eight inches, the increase was 12.2 per cent at two inches (aorta, 4.2 inches), and 18.9 per cent at four inches (aorta, 6.2 inches).

8. Inasmuch as the magnification is dependent upon object-film distance and target-film distance, the variation of the former in different parts of the heart and aorta would cause an unequal distribution of the magnification, and, therefore, the shape would be altered. The distortion of the heart is not great and is of little practical significance. The aorta, however, may be considerably magnified and distorted, especially in deep chests, in which the object-film distance of the descending aorta is increased.

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A COMPARATIVE STUDY OF NORMAL AND ABNORMAL BLOOD PRESSURES AMONG UNIVERSITY STUDENTS, INCLUDING THE COLD-PRESSOR TEST*

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MANY cases of hypertension and hypotension are of obscure origin. Consequently, the significance of these supposedly abnormal blood pressures is still vague and indefinite.

In order that a proper interpretation of abnormal blood pressure readings may be made, it is necessary to know the physiology of blood pressure. We are acquainted with most of the factors which govern blood pressure, i.e., the elasticity of the arteries, the autonomic nervous system, the rate of the heartbeat, the blood volume, and certain endocrine secretions. Pathologic conditions, such as hyperthyroidism, toxemias of pregnancy, foci of infection, tumors of the spinal cord and suprarenal gland, increased intracranial pressure, and some cases of arteriosclerosis and nephritis have been definite factors in the production of arterial hypertension. It has been known for some time that hypotension is frequently associated with such chronic, wasting diseases as tuberculosis, cancer, anemia, typhoid fever, and Addison's disease, as well as hypoadrenia, hypothyroidism, and the neurasthenic syndrome.

There are several classifications of conditions associated with high and low blood pressure, but they all agree on one group, in which all cases in which there are no apparent causative factors are placed. These patients are said to have an essential hypertension or hypotension. In other words, no apparent reason can be found for the abnormal blood pressure—at least with our present knowledge of the subject.

This investigation was undertaken in order to study the normal and apparently abnormal blood pressures among university students. A history and physical examination was obtained on each entering student. This study included observations on 15,500 male students at the University of Illinois, from 1935 to 1939. Those with high or low blood pressure, as well as normal controls, were re-examined at intervals, and the following information obtained from them:

Name__________________. Class_________. Wt._________. Pulse________.
Date of entrance_____________. Blood pressure_______. Duration_______.
Age___________. Ht.___________. Descent_________________.
Family history (particularly pertaining to cardiovascular disease, high and low blood pressure).
Illness______________________. Operations_________________________.
Work—Mental______________________, Physical____________________.
Habits—Eating rate__________________, Amount eaten_________________.
Bowels____________________. Weight change__________________.
Amount of exercise____.

*From the University of Illinois Health Service Department, Urbana.
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Amount of sleep................ Emotions...............
Use of coffee (over 1 cup daily)............................
Tobacco (more than 6 cigarettes, pipes, chews)............
Physical examination

The students with a systolic blood pressure of more than 150 mm. Hg at the time of their entrance examination were put into the hypertension group. All students with a systolic pressure, upon entrance, below 108 were classified, for this investigation, as having hypotension. The normal, or control, group consisted of matriculants with a systolic blood pressure between 114 and 138 mm. Hg. The cold-pressor test was not done in discernible cases of organic heart, kidney, or thyroid disease.

The cold-pressor test technique, as described by Hines and Brown,[1] was used to study the vasomotor reactions of ninety-six hypertensive, 128 normal, and fifty-six hypotensive, subjects. Two variations of this technique were made. The hand was kept in ice water until the maximum rise in blood pressure was reached. It required about three minutes, in a few cases, to reach the peak. Thirty students were tested in the reclining position, according to the method of Hines and Brown. These same students were also tested in the sitting position. A comfortable chair was provided, with a table of convenient height on one side for the sphygmomanometer, and a stool on the other side for the ice water container. Following the rest period, it was found that the basal blood pressure readings and the response to the cold-pressor test in the two positions checked with each other. Consequently, the remaining tests were all done with the subject in the sitting position. This position has the advantage of making the test available to all physicians, even in small offices in which facilities for carrying out the test in a reclining position are inadequate. Most examining tables are too hard and uncomfortable to be used for this type of study.

A comparative study of the three groups revealed that 73 per cent of the subjects with normal blood pressure showed the maximum systolic increase within one minute, whereas only 49.9 per cent of the hypertensive and hypotensive groups showed the maximum response within that time (Table I). By the end of two minutes, all of the normal and hypotensive subjects had attained this maximum increase, as compared to 86.8 per cent of the hypertensive group. It will be noted that the diastolic pressures in the three groups closely paralleled the systolic pressures.

Another interesting aspect of this vasomotor response to the cold test was that the systolic pressure of only 24.4 per cent of the hypertensive subjects increased from 1 to 10 mm. Hg, as compared to 63 per cent and 41.6 per cent of the normal and hypotensive subjects, respectively (Table II). Seventeen and seven-tenths per cent of the hypertensive group showed increases ranging from 21 to 30 mm. Hg, in contrast to 7.4 per cent of the normal subjects and none of the hypotensive group. The average maximal increase in the systolic pressure in the hypertensive, normal, and hypotensive groups was 18, 10.4, and 11 mm. Hg, respectively. The diastolic pressure increased about the same as the systolic pressure, with the exception that, in the normal group, the diastolic pressure increased, on the average, 3.3 mm. Hg more than the systolic pressure.

TABLE I

TIME REQUIRED FOR MAXIMUM RESPONSES OF BLOOD PRESSURE TO COLD TEST

BLOOD PRESSURE	TIME IN MINUTES						
	½	1	1½	2	2½	3	4
High							
Systolic	15.2*	34.7	4.3	32.6	4.4	9.7	
Diastolic	26.6	17.7	8.8	31.0	4.4	8.8	2.2
Normal							
Systolic	46.1	26.9	19.2	7.7			
Diastolic	19.2	34.6	15.3	26.9	3.8		
Low							
Systolic	8.3	41.6	8.3	41.6			
Diastolic	8.3	41.6	0	41.6	8.3		

*All figures represent per cent of subjects studied.

TABLE II

THE INCREASE OF THE SYSTOLIC BLOOD PRESSURE IN RESPONSE TO THE COLD TEST

BLOOD PRESSURE	MM. OF HG INCREASE					
	0	1-10	11-20	21-30	31-40	AVERAGE INCREASE
High						
Systolic	2.2*	24.4	46.6	17.7	8.8	18.0
Diastolic	2.3	26.7	26.7	37.3	6.9	17.0
Normal						
Systolic	3.7	63.0	25.9	7.4	0	10.4
Diastolic	11.1	33.3	33.3	14.8	7.4	13.7
Low						
Systolic	0	41.6	58.3	0	0	11.0
Diastolic	0	50.0	50.0	0	0	11.0

*All figures represent per cent of subjects studied, except last vertical column, which gives Mm. Hg.

The systolic pressures in the normal group had a definite tendency to return to the basal level faster than in the hypertensive and hypotensive groups (Table III). Within three minutes after the cold test was begun, the systolic pressures of 62.8 per cent of the normal subjects had returned to the basal level, as compared to only 31 per cent and 24.9 per cent, respectively, of the hypertensive and hypotensive subjects. In fact, seven to eight minutes elapsed before the systolic pressures of all subjects in the latter groups returned to their initial level. Ninety-six and two-tenths per cent of the diastolic pressures in the normal group returned to the basal level within four minutes, as compared to 56.7 per cent and 58.2 per cent, respectively, in the hypertensive and hypotensive groups.

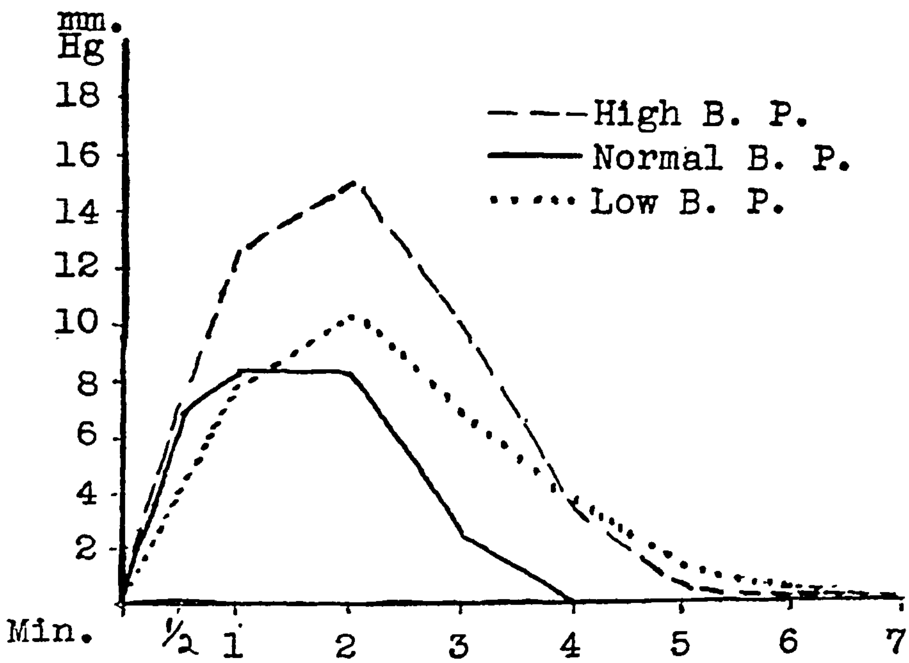
From Graphs I and II, which record the average increase in the systolic and diastolic pressures, and the duration of the increase, for each group, it is apparent that:

1. The hypertensive and hypotensive subjects were slower in reaching their maximum increase in the systolic and diastolic pressures.
2. There was a greater increase in the systolic and diastolic pressures of the hypertensive subjects than in the control group.

3. The hypertensive and hypotensive subjects returned to their basal level more slowly than did the normal subjects.

Hines and Brown[1] observed no relationship between sensitivity to ice water and blood pressure response. They explain the mechanism as a widespread vasomotor reaction initiated through the neurogenic arc. According to these authors, the reaction is not mediated by an adrenal hormone, for it occurs in adrenalectomized dogs and in Addison's disease, and, also, when a tourniquet is placed around the arm which is in the ice water. They found that the maximum response usually occurred within the first thirty seconds, and, in normal subjects, that the blood pressure returned to the basal level within two minutes. In the present investigation, the maximum response usually occurred between one and two minutes, after which the pressure dropped to the basal level in the normal group in about four minutes (Graph I). Just why there should be this difference is not clear, unless age is a factor. The ages of these students ranged from 17 to 24 years.

Table IV summarizes the averages of the blood pressure observations.

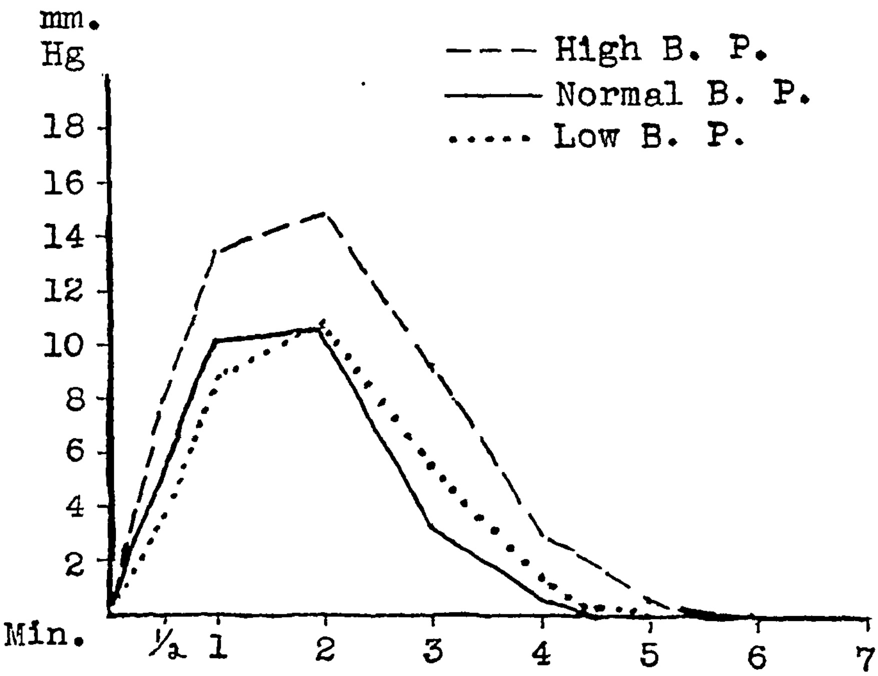


Graph I.—Increase in the systolic blood pressure during the cold test.

In the vertical column, designated as mm. Hg, there are, for each group, the average basal, usual, and maximum blood pressure increases produced by the cold test. The usual blood pressure was determined by the average of repeated measurements before subjects began the rest period prior to the cold test. The differences between the usual and basal systolic blood pressure in the hypotensive and normal groups were only 5 and 7 mm., respectively, in contrast to a difference of 28 mm. in the hypertensive group. There was a difference between the basal and

usual systolic pressure in the hypertensive group of 10 mm. more than the maximum increase produced by the cold test. This marked variation between the basal level and the usual pressure is a definite aid in detecting hyperreactors, particularly when it is confirmed by the results of the cold test. The diastolic pressure response to the cold test in the three groups was approximately the same as that of the systolic blood pressure. The difference between the basal and usual diastolic pressures in the hypertensive group was far below the difference noted in the systolic pressures.

The detailed histories obtained from the students in this investigation brought forth some interesting points (Table V). Forty-three and seven-



Graph II.—Increase in the diastolic blood pressure during the cold test.

tenths per cent of the hypertensive subjects, as compared with only 11.7 per cent and 14.3 per cent, respectively, of the normal and hypotensive subjects, stated that they were nervous or easily excited. A family history of hypertensive cardiovascular disease was obtained from 54.1 per cent of the hypertensive subjects, as contrasted with 3.1 per cent in the normal, and 5.3 per cent in the hypotensive, groups. It was also noted that 17.8 per cent of the hypotensive subjects gave a history of familial hypotension, whereas none of the hypertensive subjects, and only 2.3 per cent of the normal subjects, indicated that members of their immediate family or of preceding generations had had low blood pressure.

Hines[2] and Brown[3] noted that a family history of hypertensive cardiovascular disease was five times as frequent among persons who had high

TABLE III

TIME REQUIRED FOR BLOOD PRESSURE TO RETURN TO BASAL LEVEL DURING COLD TEST

BLOOD PRESSURE	TIME IN MINUTES								
	0	1	2	3	4	5	6	7	8
High									
Systolic	2.2*	0	4.4	24.4	22.2	29.0	11.1	4.2	2.2
Total†	2.2	2.2	6.6	31.0	53.2	82.2	93.3	97.5	99.7
Diastolic	2.2	0	0	20.5	34.0	27.2	16.0		
Total	2.2	2.2	2.2	22.7	56.7	83.9	99.9		
Normal									
Systolic	3.7	3.7	11.0	44.4	29.6	3.7	3.7		
Total	3.7	7.4	18.4	62.8	92.4	96.1	99.8		
Diastolic	11.1	7.4	11.1	37.0	29.6	0	3.7		
Total	11.1	18.5	29.6	66.6	96.2	96.2	99.9		
Low									
Systolic	0	0	8.3	16.6	16.6	25.0	25.0	8.3	
Total	0	0	8.3	24.9	41.5	66.5	91.5	99.8	
Diastolic	0	0	0	41.6	16.6	25.0	16.6		
Total	0	0	0	41.6	58.2	83.2	99.8		

*All figures represent per cent of subjects studied.
†Accumulative total for each successive minute.

TABLE IV

SUMMARY OF BLOOD PRESSURE VARIATIONS FROM THE BASAL LEVEL

	SYSTOLIC BLOOD PRESSURE						DIASTOLIC BLOOD PRESSURE					
	L. B. P.*		N. B. P.*		H. B. P.*		L. B. P.		N. B. P.		H. B. P.	
	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG	MM. HG	RISE MM. HG
Basal B. P.	99		116		136		70		74		80	
Usual B. P.	104	5	123	7	164	28	75	5	77	3	87	7
B. P. with Cold Test	110	11	126	10	154	18	81	11	88	14	96	16

*L. B. P. indicates low blood pressure group.
N. B. P. indicates normal blood pressure group.
H. B. P. indicates high blood pressure group.

blood pressure or were hyperreactors to the cold test as it was among subjects who reacted normally to the test. The results in Table V certainly compare favorably with those of these authors. It was suggested long ago that a tendency to essential hypertension might possibly be hereditary. Recent, concrete evidence has substantiated this belief. The type of blood pressure reaction in many cases follows a definite hereditary pattern, whether it be high or low. Perhaps this depends, for the most part, upon some structural or physiologic peculiarities of the autonomic nervous system or endocrine system which are passed through the germ plasm from one generation to the next.

The quantity of food eaten may have something to do with hypertension, for there were well over twice as many heavy eaters in the hypertensive group as in the other two groups. The amount of exercise, apparently, is not a factor in the production of essential hypertension.

TABLE V

DETAILS OF HISTORIES OF SUBJECTS OF THIS STUDY

	PER CENT WITH H. B. P.*	PER CENT WITH N. B. P.*	PER CENT WITH L. B. P.*
Emotions			
Nervous and excitable	43.7	11.7	14.3
Stable	56.3	88.2	85.7
H.B.P. in family	51.1	3.1	5.3
L.B.P. in family	0	2.3	17.8
Foci of infection on physical examination	18.7	26.5	8.9
Constipation	4.1	6.2	7.1
Rate of Eating			
Rapid	44.7	11.7	42.8
Moderate	41.6	76.6	50.0
Slow	13.5	11.7	7.1
Quantity Eaten			
Heavy eater	35.4	14.8	14.3
Medium eater	63.5	78.9	78.5
Light eater	1.1	6.2	7.1
Exercise			
Vigorous	6.2	6.2	7.1
Moderate	40.6	35.1	50.0
Mild	53.1	58.5	42.8
Stimulants			
Tobacco	16.6	19.5	50.0
Coffee	12.5	11.7	28.5

*H. B. P. indicates high blood pressure.
N. B. P. indicates normal blood pressure.
L. B. P. indicates low blood pressure.

Tobacco (more than six cigarettes, cigars, pipes, or chews) and coffee (more than one cup daily) were used by two to three times as many students in the hypotensive group as in the other two groups.

Patients are frequently told, after the first measurement, that they have high or low blood pressure. Note that the blood pressure of 64.8 per cent of the students who had a systolic pressure above 150 mm. at the time of their entrance physical examination was normal at the time of the first re-examination. After the third blood pressure measurement, 75 per cent were well within normal limits (Table VI). Many of these students were hyperreactors to the cold test, but, in the present state of our knowledge, by far the most of them must still be considered normal. Certainly, excitement, nervousness, a sense of uncertainty, new environmental adjustments, or other psychologic factors must have had something to do with producing most of these high systolic blood pressure readings. Reisman[4] believes that economic and domestic worries may cause a temporary or permanent rise of blood pressure. Grollman[5] found that an increase in the pulse rate and blood pressure occurred following psychic disturbances. Just how this action occurs is still a matter of conjecture. Does an increase in the secretion of adrenalin or pituitrin take place? Does the autonomic nervous system produce a spastic constriction of the arterioles, or can it be explained by the intrinsic myogenic

capacity of the blood vessels to contract and dilate? When the hypotensive subjects returned for their re-examination, 82.2 per cent were within normal limits (Table VI).

TABLE VI

STUDENTS WITH ABNORMAL SYSTOLIC BLOOD PRESSURE UPON ENTRANCE PHYSICAL EXAMINATION AND RESULTS OF SUBSEQUENT EXAMINATIONS

BLOOD PRESSURE	ABOVE 150 MM. HG UPON ENTRANCE		BELOW 104 MM. HG UPON ENTRANCE	
	NO. OF STUDENTS	PER CENT OF STUDENTS	NO. OF STUDENTS	PER CENT OF STUDENTS
Remained unchanged	96	24.8	56	17.6
To normal at first recheck	251	64.8	192	60.5
To normal at second recheck	25	6.4	69	21.7
To normal at third recheck	15	3.9	0	0
Total rechecked	387		317	
Not rechecked	132	25.4	74	18.9
Total	519		391	

The most important factor controlling blood pressure centers around the autonomic nervous system. When the sympathetics and parasympathetics are in a state of balance, a normal pressure results. When the impulses over the nervous pathways to the heart are in balance, the heart beats regularly and at a normal rate. If this equilibrium is disturbed, the heart rate changes, and the change depends upon which pathway carries the greater number of impulses. So it is with blood pressure; if this balance is disturbed, a hypertonic or hypotonic state occurs, and more impulses or impulses of greater intensity are sent over the vasopressor or vasodepressor nerve fibers, as the case may be. Whether this regulation is governed by the carotid sinus, or initiated through the neurogenic arc, or by an intrinsic myogenic factor, or entirely by hormonal stimulation, or by unknown regulatory centers has not been established definitely. A combination of these factors may be operative. Some evidence has been produced by Zipf[6] and Goerner and Haley[7] that depressor substances may also be present in the body fluids. DeGroat and his associates,[8] experimenting on animals, were able to produce hypertension by denervating the carotid sinuses and sectioning the depressor nerves.

SUMMARY

The blood pressure reactions to a standard cold stimulus of students with high, normal, and low blood pressure were noted. A careful history, physical examination, and re-examination were obtained on students with normal and abnormal blood pressure.

1. With the application of the standard cold test, the normal subjects reached the maximum increase in the systolic and diastolic blood pressure sooner than the hypertensive and hypotensive subjects.

2. There was a greater increase in the systolic and diastolic blood pressure in the hypertensive group than in the control group.

3. The blood pressure of the hypotensive and hypertensive subjects returned to the basal level more slowly than did that of the normal subjects.

4. There was a far greater difference between the usual systolic blood pressure and the basal blood pressure in the hypertensive group than in the normal and hypotensive groups. This criterion is a definite aid in discovering hyperreactors, especially when it is confirmed by the cold test.

5. The same factors which govern the emotional status of individuals play an important part in their blood pressure reactions.

6. There is a definite hereditary factor in the regulation of blood pressure. The tendency toward essential hypertension or hypotension is carried by the germ plasm from one generation to the next.

7. The percentage of heavy eaters in the hypertensive group was over twice as great as in the normal and hypotensive group.

8. The amount of work or exercise is apparently not an etiologic factor in the production of essential hypertension.

9. Tobacco and coffee were used by two to three times as many students in the hypotensive group as in the other two groups.

10. At least two or three subsequent examinations should be made before a person is classified as having hypertension or hypotension. This will prevent worry and anxiety in certain cases, and will be of definite value to the physician in arriving at a definite diagnosis.

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STUDIES IN HYPERTENSIVE HEART DISEASE

IV. Factors in the Production of Congestive Failure

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IT IS known that a number of factors may contribute to heart failure in the course of hypertensive heart disease. The relative importance of these factors, however, has not been established. It is maintained, on the one hand, that myocardial weakness in hypertensive heart disease is due primarily to factors resulting from the hypertension itself, and, on the other, to concomitant coronary disease. The purpose of the present study is to throw some light on the relative importance of these factors.

METHOD

It appeared that the significance of the hypertensive factors could best be evaluated by comparing the cardiac abnormalities in this type of heart failure with those in cases in which there was no hypertension. Therefore, two groups of patients were studied: 137 with hypertension, and 324 without hypertension. Patients were considered to have hypertension when their systolic and diastolic pressures were consistently above 150 and 90 mm. of mercury, respectively. Patients with congestive failure associated with diabetes, thyrotoxicosis, anemia, pregnancy, uncontrolled auricular fibrillation, and heart disease of congenital, rheumatic, or syphilitic origin were excluded. Congestive failure was present in forty-nine of the patients with hypertension, and in thirty-one of the patients who did not have hypertension. Among the latter there were six cases of cor pulmonale, with extensive pulmonary disease, right ventricular failure, and hypertrophy of the right ventricle (necropsy). These were considered as probably examples of hypertension of the lesser circulation, and were therefore excluded. There remained, for comparison, twenty-five patients without hypertension. In each case the diagnosis of congestive failure was based either on a history of attacks of cardiac asthma or pulmonary edema, or on objective evidence, such as prolongation of the circulation time, râles at the bases of the lungs, peripheral edema, enlargement of the liver, and accumulations of fluid in the serous cavities. Rigid criteria were used in the classification of the degree of coronary artery disease. The atherosclerosis was considered slight when the intimal changes were few and scattered, or entirely absent; as moderate, when the intimal surfaces were covered with many plaques, but the process had produced but little or no narrowing of the lumen; and as marked, when there was extreme narrowing or occlusion of the major branches.*

Patients Without Hypertension.—Marked coronary disease was present in twenty-three of the twenty-five patients without hypertension (90 per cent). Nineteen of these had occlusion of one major coronary artery,

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*Major branches refer to main stems of left anterior descending, left circumflex, and right coronary arteries.

and fifteen had an occlusion of one, with marked narrowing or occlusion of at least one other, major artery (Table II). In two cases (24, 25) the heart failure was apparently not caused by coronary disease. One of these patients (24) showed a slight degree of atherosclerotic aortic stenosis, and this may have contributed to his heart failure.

It will be noted that five of the patients in this group showed varying degrees of atherosclerotic aortic stenosis (Table II). Four of these also showed marked coronary disease. If we exclude these five patients from the series, nineteen of the remaining twenty patients (95 per cent) showed marked coronary disease, and sixteen (80 per cent) had occlusions of one or more major branches.

TABLE I

PATIENTS WITH CONGESTIVE FAILURE

DATA	WITH HYPERTENSION		WITHOUT HYPERTENSION	
TOTAL NUMBER OF CASES	49	100%	25	100%
Age Distribution				
30-49 years	5	10.2%	0	-
50-59 years	10	20.4%	6	24.0%
60-69 years	21	42.8%	10	40.0%
70- years	13	26.6%	9	36.0%
Sex:				
Males	38	77.6%	22	88.0%
Females	11	22.4%	3	12.0%
Severe Coronary Disease	26	53.1%	23	90.0%
Moderate Coronary Disease	16	32.7%	2	8.0%
Slight Coronary Disease	7	14.2%	0	-
Patients with Coronary Occlusion	16	32.7%	19	76.0%
Patients with Cardiac Infarction	10	20.4%	14	56.0%
Old Infarcts	5	10.2%	12	48.0%
Recent Infarcts	5	10.2%	2	8.0%
Patients with Cardiac Asthma	27	55.1%	5	20.0%
Patients with Angina Pectoris	22	44.9%	12	48.0%
Angina Pectoris prior to C.F.	18	36.7%	11	44.0%
Angina Pectoris after C.F.	4	8.2%	1	4.0%
Duration of Cardiac Symptoms				
Less than 1 year	5	10.2%	4	16.0%
1-5 years	27	55.1%	14	56.0%
5-10 years	17	34.7%	7	28.0%
Duration of Congestive Failure				
Less than 6 months	24	49.0%	8	32.0%
6 months to 2 years	17	34.7%	15	60.0%
Over 2 years	8	16.3%	2	8.0%

Patients With Hypertension.—Twenty-six of the forty-nine patients with hypertension and congestive failure had marked coronary disease. Sixteen of these had occlusion of one major coronary branch, and ten had an occlusion of one, with marked narrowing or occlusion of at least one other, major artery (Table III). The degree of coronary disease in twenty-three cases (47 per cent), however, was classified as slight or moderate, for in these cases there was no demonstrable interference with the circulation through the major coronary arteries. The heart weights

TABLE II

PATIENTS WITHOUT HYPERTENSION MANIFESTING CONGESTIVE FAILURE

NO.	AGE	SEX	HEART WEIGHT GM.	DEGREE COR. DIS.	VESSELS OCCLUDED			INFARCTS		ANGINA PECTORIS	CARDIAC ASTHMA	CLINICAL C.T.	DURATION OF SYMPTOMS	DURATION OF FAILURE
					L.A.D.	L.C.	R.C.	OLD	RECENT					
1	90	F	490	3	N	0	N	0	0	0	0	0	2 weeks	2 weeks
2	80	M	620*	3	+	N	+	0	0	0	0	0	4 years	Few wk.
3	88	M	420	3	+	N	N	0	0	0	+	0	Few yr.	2 yr.
4	68	F	310	3	N	0	0	0	0	0	0	0	Several yr.	1 week
5	85	M	530	3	N	0	N	#	#	+	0	0	4 mo.	6 wk.
6	82	F	580*	3	0	N	0	0	0	0	0	0	2 yr.	3 mo.
7	80	M	530	3	+	0	0	0	0	+	0	+	4 yr.	3 yr.
8	74	M	720*	3	+	0	0	+	0	0	0	0	3 yr.	7 mo.
9	67	M	540	3	+	N	N	+	0	+	0	+	5 yr.	2 yr.
10	65	M	450	3	+	N	0	+	0	+	0	+	4 yr.	2 yr.
11	68	M	580	3	+	+	+	#	#	+	0	+	5 yr.	3 yr.
12	62	M	500	3	+	+	0	#	#	+	0	+	9 yr.	14 mo.
13	60	M	420	3	+	N	N	0	+	+	+	+	1 mo.	1 mo.
14	63	M	520	3	+	0	0	0	0	0	0	0	1 yr.	1 yr.
15	63	M	620	3	N	+	0	+	0	+	+	0	2½ yr.	2 yr.
16	55	M	860*	3	0	+	+	0	0	0	0	0	2½ yr.	2 yr.
17	59	M	500	3	N	N	+	+	0	+	0	+	9 yr.	2 yr.
18	58	M	530	3	0	0	+	+	0	0	0	+	14 mo.	14 mo.
19	58	M	520	3	N	N	+	+	0	0	0	0	5 yr.	2 yr.
20	55	M	490	3	+	N	+	0	+	+	0	+	3 mo.	3 mo.
21	75	M	400	3	+	+	0	+	0	0	+	0	Several yr.	6 mo.
22	56	M	Large	3	+	+	0	+	0	+	+	+	2 yr.	1½ yr.
23	64	M	520	3	0	+	+	+	0	+	0	+	2 yr.	2 yr.
24	77	M	740*	2	0	0	0	0	0	0	0	0	Few yr.	1½ yr.
25	66	M	440	2	0	0	0	0	0	0	0	0	1 yr.	4 mo.

* = Atherosclerotic aortic stenosis.
# = Myocardial fibrosis.
C.T. = Coronary thrombosis.
N = Extreme narrowing.
L.A.D. = Left anterior descending.
L.C. = Left circumflex.
R.C. = Right coronary.
1 = Slight coronary disease.
2 = Moderate coronary disease.
3 = Marked coronary disease.

in fourteen cases were above 600 grams; in five others, between 450 and 600 grams; and, in the four remaining cases (6, 7, 11, 12) 340 to 400 grams. Three of these patients were elderly women whose failure was of short duration. One (12) was a 75-year-old man whose heart weighed 400 grams and was the seat of considerable diffuse myocardial fibrosis.

It is possible that in cases in which the heart weighed 400 grams, or less, the load of the hypertension was not a major factor in the cause of congestive failure. If we exclude such cases from our series, and, in addition, the two cases (14, 20) of aortic stenosis of arteriosclerotic origin, there remain seventeen out of a total of forty-two cases (40 per cent) in which congestive failure developed without significant coronary disease.

Comparison of Patients With, and Patients Without, Hypertension.—Excluding the patients with atherosclerotic aortic stenosis and those with small hearts whose hypertension might be only a questionable factor, coronary disease was present in 95 per cent of the patients without hypertension, and in 60 per cent of those with hypertension. Actual occlusion of at least one major artery was found in 80 per cent of the patients without hypertension, and in only 38 per cent of those with hypertension. Thus, the difference in the incidence of marked coronary disease in these two groups is striking.

The incidence of myocardial infarction in both groups of cases is in accord with the above observations. In the nonhypertensive group there were infarcts in thirteen cases (65 per cent); in the hypertensive group, in ten cases (24 per cent).

DISCUSSION

The data presented indicate that congestive heart failure unassociated with hypertension or valvular disease is primarily the result of coronary insufficiency. The high incidence of coronary disease in cases of essential hypertension naturally raises questions concerning the role of this factor in hypertensive heart failure. Averbuck[1] studied this condition in cases of hypertension with and without cardiac failure, and concluded that coronary disease was the most important factor in 90 per cent of his patients. We find a much lower incidence. In spite of the high incidence of coronary disease in cases of essential hypertension,[2] patients with heart failure caused by hypertension had much less coronary disease than patients with heart failure unassociated with hypertension. This is apparently due to the fact that in cases of hypertension other causes operate to produce myocardial weakness long before coronary disease has advanced to the stage observed in patients without hypertension. A comparison of the incidence of coronary occlusion, marked coronary narrowing, and myocardial infarction in patients with, and without, hypertension shows the extent to which

TABLE III

PATIENTS WITH HYPERTENSIVE HEART DISEASE MANIFESTING CONGESTIVE FAILURE

NO.	AGE	SEX	HEART WEIGHT GM.	DEGREE COR. DIS.	VESSELS OCCLUDED L.A.D.	VESSELS OCCLUDED L.C.	VESSELS OCCLUDED R.C.	INFARCTS OLD	INFARCTS RECENT	ANGINA PECTORIS	CARDIAC ASTHMA	CLINICAL C.T.	DURATION OF SYMPTOMS	DURATION OF FAILURE
1	63	M	600	1	0	0	0	0	0	+	0	0	2 years	1 year
2	55	M	700	1	0	0	0	0	0	0	0	0	3 years	3 years
3	64	M	550	1	0	0	0	0	0	0	+	0	1½ yr.	1½ yr.
4	68	F	475	1	0	0	0	0	0	0	+	0	Several yr.	1 wk.
5	64	M	840	1	0	0	0	0	0	+	0	0	Several yr.	4 yr.
6	63	F	360	1	0	0	0	0	0	+	0	0	3 yr.	3 mo.
7	83	F	400	1	0	0	0	0	0	0	+	0	Few yr.	2 mo.
8	59	F	630	2	0	0	0	0	0	0	+	0	Few yr.	1 yr.
9	40	M	540	2	0	0	0	0	0	0	+	0	Few yr.	2 wk.
10	68	M	620	2	0	0	0	0	0	+	+	0	2 yr.	1 yr.
11	72	F	340	2	0	0	0	0	0	0	0	0	Few yr.	9 mo.
12	75	M	400	2	0	0	0	#	#	+	0	?+	19 yr.	1 yr.
13	71	F	520	2	0	0	0	0	0	0	0	0	4 yr.	1 yr.
14	77	M	800*	2	0	0	0	0	0	+	+	0	1 yr.	4 mo.
15	62	M	700	2	0	0	0	0	0	0	0	0	4 yr.	3 yr.
16	69	M	600	2	0	0	0	0	0	0	0	0	1 yr.	1 yr.
17	68	M	740	2	0	0	0	0	0	0	+	0	2 yr.	2 yr.
18	63	M	640	2	0	0	0	0	0	+	+	+	5 yr.	2 yr.
19	60	M	600	2	0	0	0	0	0	0	+	0	2 yr.	2 yr.
20	58	M	600*	2	0	0	0	0	0	0	+	0	1 yr.	2 mo.
21	55	M	670	2	0	0	0	0	0	0	+	0	2 yr.	1½ yr.
22	38	M	630	2	0	0	0	0	0	0	+	0	4 yr.	1 yr.
23	58	M	450	2	0	0	0	0	0	+	0	0	4 mo.	24 hours
24	43	M	650	3	+	+	0	#	#	+	+	+	4 mo.	3 mo.
25	59	M	610	3	+	+	+	0	0	+	0	+	9 yr.	1 mo.
26	52	M	880	3	+	0	0	0	+	+	0	+	8 yr.	2 mo.

TABLE III—CONT'D

27	64	M	510	3	+	0	+	#	#	+	0	+	8 yr.	1 mo.
28	84	M	580	3	N	+	0	0	+	+	0	+	1 yr.	1 yr.
29	45	M	670	3	N	0	N	0	0	+	0	0	6 mo.	1 mo.
30	54	F	480	3	+	0	N	+	0	+	+	0	8 yr.	1 yr.
31	58	M	580	3	N	0	0	0	0	0	0	0	3 mo.	1 wk.
32	59	M	1000	3	N	N	N	0	0	+	+	0	10 yr.	7 yr.
33	60	F	510	3	+	+	+	0	0	+	0	+	5 yr.	1 mo.
34	65	M	700	3	+	0	0	+	0	0	0	+	Several yr.	2 mo.
35	65	M	680	3	0	+	0	+	0	0	+	0	5 yr.	3 yr.
36	63	F	540	3	N	N	N	0	0	0	+	0	5 yr.	3 yr.
37	64	M	480	3	N	N	N	0	0	0	0	0	1 yr.	3 mo.
38	69	M	600	3	+	N	N	0	+	0	+	0	2 yr.	2 wk.
39	67	M	485	3	+	+	0	+	0	0	+	0	Few yr.	1 wk.
40	67	M	520	3	+	0	0	0	0	+	+	0	2 yr.	2 mo.
41	71	M	740	3	0	0	+	0	0	0	+	+	Few yr.	2 yr.
42	73	M	600	3	0	+	+	0	0	0	0	0	2 yr.	3 mo.
43	75	M	496	3	+	0	+	+	0	+	+	0	6 mo.	1 mo.
44	73	F	460	3	N	0	0	0	0	0	0	0	Few yr.	1 mo.
45	70	M	600	3	N	0	0	0	0	+	+	0	Few yr.	1 mo.
46	83	M	590	3	N	N	0	0	0	0	0	0	Many yr.	1 mo.
47	47	M	780	3	N	0	0	0	0	0	+	0	7 yr.	6 yr.
48	74	M	600	3	+	+	0	0	+	+	+	0	Many yr.	4 yr.
49	60	F	390	3	N	0	N	#	#	+	+	+	6 yr.	1 yr.

* = Atherosclerotic aortic stenosis.
\# = Myocardial fibrosis.
C.T. = Coronary thrombosis.
N = Extreme narrowing.
3 = Marked coronary disease.
L.C. = Left circumflex.
L.A.D. = Left anterior descending.
R.C. = Right coronary.

these other factors operate. There was little or no interference with the coronary circulation in at least 40 per cent of the patients with hypertension.

Several theories have been proposed to explain the nature of heart failure in patients who do not have an appreciable degree of coronary disease, but the extent to which these theoretical factors operate is unknown. Impairment of oxygen diffusion through a thickened muscle fiber will lead to anoxia, and, in this way, cause myocardial weakness.[3, 4] Some clinical evidence of the existence of this phenomenon was presented in a previous communication,[5] in which it was shown that angina pectoris occurs in cases of hypertension with much less coronary disease than is found in patients without hypertension. Since available data indicate that attacks of angina pectoris are caused by cardiac anoxia, it is probable that this cause of myocardial weakness is an important one. In hypertension, however, there is the additional factor of increased cardiac work, and it is difficult to separate this from that of hypertrophy, per se. The final heart weight at necropsy is not a reliable index of the latter handicap, for heart failure itself is a stimulus to hypertrophy,[6] and the degree attained before failure sets in is obscured by the increase that follows in its course. In addition to anoxia resulting from coronary disease, cardiac hypertrophy, and increased cardiac work, direct muscle injury may play an important part in the heart failure of hypertensive origin. Eyster[7] maintains that hypertrophy itself is evidence of such injury, and there are many data to support this thesis. If so, the sequence of events leading to congestive failure in hypertensive heart disease without marked coronary disease might be as follows: increased cardiac work, direct muscle fiber injury, hypertrophy, anoxia resulting from both hypertrophy and increased cardiac work, muscle injury of anoxic origin, congestive failure, cardiac hypertrophy resulting from congestive failure, and further anoxia and muscle injury.

SUMMARY AND CONCLUSIONS

1. The anatomic changes in forty-nine patients with hypertension and twenty-five patients without hypertension, all of whom had congestive failure, were compared.

2. In the nonhypertensive (nonvalvular) group, marked coronary disease was present in twenty-three (90 per cent); occlusion of the major coronary arteries in nineteen (76 per cent); and myocardial infarcts in fourteen (56 per cent).

3. In the hypertensive group, marked coronary disease was present in twenty-six (53 per cent), coronary occlusion in sixteen (33 per cent), and infarction in ten (20 per cent).

4. Factors other than coronary disease play an important part in heart failure of hypertensive origin in at least 40 per cent of cases.

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Corrigendum

In the article entitled "Variations in Normal Precordial Electrocardiograms," by Ralph L. Shanno, M.D., which appeared in the June, 1940, issue of the Journal, the beginning of line 18, page 716, should read "to −22 mm.," instead of "to +22 mm."

Department of Clinical Reports

COMPLETE COARCTATION OF THE AORTA

A Case Report

Samuel Gitlow, M.D., and Robert I. Sommer, M.D.
Bronx, N. Y.

HISTORY.—W. Mc., a white man, 45 years of age, was admitted to the medical service of Dr. William Weinberger, at Lebanon Hospital, with symptoms of cardiac failure (viz., dyspnea, edema, and fatigability). He had had little cardiac disability until two years before admission, although he had been apprised of his cardiac disease when he was examined for the army, in 1917. In 1927, he was observed at a veterans' hospital, and there operated upon for appendicitis. He was again told of his heart disease, that his heart was enlarged, and that the vessels in his neck were pulsating. He was an athletic automobile salesman of moderate habits.

His first signs of decompensation appeared two years prior to admission. With rest in bed and other treatment, this cleared up in a few weeks, and he was able to continue his work until five months before admission, when decompensation again set in. At the same time he developed bronchopneumonia and hydrothorax, for which he was treated at a hospital. Thence he was transferred to another hospital, where roentgenologic study revealed coarctation of the aorta. He was discharged feeling fairly well, but two months later again became acutely decompensated and was admitted to the Lebanon Hospital. The patient had had syphilis for a year; ten blood Wassermann reactions had been positive, and he had received antisyphilitic treatment.

Physical Examination.—The patient was an emaciated, middle-aged man, suffering from acute dyspnea. There were marked pulsations in both supraclavicular regions, in the left infraclavicular region, under the left scapula, and between several of the ribs. There was a large artery, about one-fourth inch in diameter, coursing across the left scapula from above downward. The heart was enlarged to the left and to the right. A loud, blowing, systolic murmur was heard all over the precordium; its maximum intensity was at the left sternal border in the second intercostal space. Gallop rhythm was present. There was congestion of the lungs. The liver was felt 4 cm. below the costal margin. The spleen was also palpable. The blood pressure was 170/88 (mercury manometer) in the upper extremities, and 110/50 in the lower extremities.

Laboratory Examination.—The blood Wassermann reaction was weakly positive (one plus).

The gonococcus complement fixation was twice positive. Roentgenograms showed rather marked notchings on the under surfaces of the ribs posteriorly (Fig. 1). The arch of the aorta was small and not definitely outlined, and the descending aorta was not visualized in the left oblique position. The trachea was displaced to the right. The electrocardiogram revealed an intraventricular conduction disturbance of the arborization block type. A clinical diagnosis of coarctation of the aorta was made by one of us because of the evidence of col-

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From the Medical Service of Dr. William Weinberger, Lebanon Hospital, Bronx, N. Y.
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lateral circulation. Roentgenologic examination confirmed the diagnosis. Treatment consisted of rest in bed, digitalis, etc. The patient died fifteen days following admission.

Autopsy.—Autopsy revealed a tremendously hypertrophied heart, weighing 1200 grams. The aortic valve was congenitally bicuspid and did not admit a small finger because of inrolling, thickening, and calcification. One of the cusps was covered with fresh blood clots. The aortic arch showed little atherosclerosis. The ascending aorta was moderately enlarged, and, immediately after the point at which the subclavian came off, the aorta narrowed and ended in a complete stenosis in the region of the ductus arteriosus (Fig. 2). The aorta continued distal to the occlusion, although it was somewhat narrowed. The aorta gave off very large innominate, left common carotid, and left subclavian arteries. The iliacs were very large, and took their blood supply from the superior and inferior epigastric arteries, which were direct continuations of extremely large internal mammary arteries. The ribs which were notched posteriorly could not be dissected out because of autopsy limitations. Interesting enough was the fact that there were no reverent microscopic changes, and no evidences of syphilis or rheumatic heart disease.

Fig. 1.—Roentgenogram showing the notchings of the inferior border of the ribs. Note widening of the aortic arch.

COMMENT

Our case is one of complete stenosis of the isthmus of the aorta. Of 200 cases of coarctation reported in the literature,[1] in only forty-seven was the stenosis complete. Further interesting features of our case were a congenitally bicuspid aortic valve and calcareous stenosis of the aortic valve of the Moenckeberg type. These anomalies are not infrequently found in conjunction with coarctation of the aorta. Maude Abbott[1] reports the presence of bicuspid valves in 25 per cent of all cases of coarctation, and in ten cases in which complete stenosis

was present. The combination of bicuspid valve and coarctation is important clinically, because there is a *locus minoris resistentiae* to the invasion of infectious processes which may predispose to a variety of conditions, such as mycotic aneurysm, aortic valvular disease, and myocardial disease. Bacterial inflammations have a predilection for the crevices of the composite cusps. This is sometimes referred to as the "commissural lesion of Lewis and Grant." In half of the cases of rupture of the aorta the aortic valve is bicuspid.

The aortic stenosis in our case is not to be considered as congenital, but rather as acquired, and, in this case, as a probable cause of heart failure. Moenckeberg stated that degenerative lesions in the aortic valve may begin at 35, almost as a physiologic process. Bishop and co-workers,[2] in their article on stenosis of a bicuspid aortic valve, note that one of the causes of aortic stenosis is a congenitally defective cusp,

Fig. 2.—Coarctation of the aorta—arrows pointing to the complete stenosis. (Note enlarged ostia of the intercostal arteries.)

with subsequent calcification. The others, of course, are of infectious origin (rheumatic and bacterial endocarditis) or are arteriosclerotic or degenerative lesions without previous inflammation.

In cases of coarctation of the aorta, the course and duration of the patient's life are wholly dependent on whether or not an adequate collateral circulation develops. There are two main routes by which a collateral circulation may establish itself; the one depends on anastomosis of the branches of the subclavian, such as the superior intercostal, postscapular, interscapular, and subscapular arteries, together with the aortic branches of the internal mammary arteries, with the first four intercostal arteries, thus carrying most of the blood into the descending aorta, and thence to the lower extremities. The second, and more circuitous, route is by anastomosis of the internal mammary arteries with the superior and inferior epigastrics, with the formation, sometimes, of tortuous, dilated vessels which often look like cirsoid aneurysms.

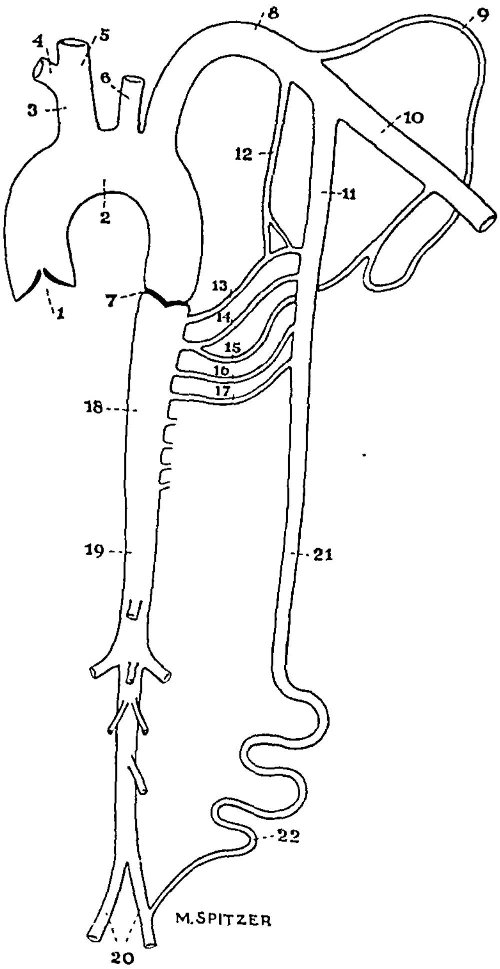

Fig. 3.—Collateral circulation. *1*, Bicuspid valve; *2*, aortic arch; *3*, innominate; *4*, right subclavian; *5*, right carotid; *6*, left common carotid; *7*, coarctation; *8*, left subclavian; *9*, subscapularis; *10*, axillary; *11*, internal mammary; *12-17*, intercostal arteries connecting with aortic intercostals; *18*, descending aorta; *19*, abdominal aorta; *20*, iliacs; *21*, superior epigastric; *22*, inferior epigastric.

In the first case, the circulation is more perfect and constant, so much so that in some instances there is no difference in pulse volume and blood pressure between the upper and lower extremities. Differences in circulation time, as demonstrated by Blumgart[3] et al., may lead to the correct diagnosis. The second, more circuitous, route is less constant and less adequate in supplying blood to the lower extremities. In this type, differences of blood pressure and circulation times between the two extremities are noted. The accompanying schema illustrates the type of collateral circulation in our case (Fig. 3).

SUMMARY

This is a case of a complete coarctation of the aorta, together with a bicuspid aortic valve and aortic stenosis of the Moenckeberg type. The history indicated that the collateral circulation had been perfectly adequate, despite the complete coarctation of the aorta. Actual impairment of the aortic outflow did not occur until after the development of stenosis of the aortic valve.

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3. Blumgart, H. L., Lawrence, J. S., and Ernstene, A. C.: The Dynamics of the Circulation in Coarctation of the Aorta of the Adult Type, Arch. Int. Med. 47: 816, 1931.

PAROXYSMAL TACHYCARDIA IN A CHILD, TREATED WITH ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL)

Bernard J. Walsh, M.D., and Howard B. Sprague, M.D.
Boston, Mass.

The infrequency with which paroxysmal tachycardia occurs in children is indicated by Taran and Jennings,[1] who found fifty-two cases in a review of the literature from 1892 to 1935. In this hospital (House of the Good Samaritan), it has been noted in five of a series of 1,000 patients. Although Stepp and Schliephake,[2] in 1925, used a choline substance with success in the treatment of paroxysmal tachycardia, it was not until after the work of Starr[3] that choline compounds came into frequent use. Stenhouse[4] has recorded his satisfactory experience with acetylcholin in the case of a boy, 14 years old, during an attack of paroxysmal auricular tachycardia which had persisted for four days despite pressure on the carotid sinuses, strophanthin intravenously, and increasing doses of quinidine. Von Kiss[5] terminated a protracted attack of auricular tachycardia with acetylcholin bromide (Tonocholin B) in the case of a 16-year-old girl. This patient had previously had many attacks which were invariably stopped by induced vomiting alone, or by the combination of quinine urethrane intramuscularly and induced vomiting. Recently, Wright[6] reported the repeated use of acetyl-beta-methylcholine chloride (Mecholyl) over a period of two years in the case of a girl, 8 years of age, during numerous attacks of paroxysmal tachycardia.

Because of the paucity of reports of favorable results from the use of acetyl-beta-methylcholine chloride in children, we have thought it worth while to present the following case. This patient is, as far as we know, the youngest of those whose paroxysmal tachycardia has been successfully treated with acetyl-beta-methylcholine chloride.

CASE REPORT

A 4-year-old boy entered the House of the Good Samaritan Dec. 9, 1937. His health had been good until three weeks before, when he developed rheumatic fever, with painful, red swelling of various joints. When he was admitted to another hospital three days after the onset of the illness, a pericardial friction rub was present, as well as murmurs indicative of rheumatic valvular disease.

When he was first seen by us, it was apparent that, although much improved, he still suffered from active rheumatic fever.

On examination, the heart was normal in size. There was a harsh systolic murmur at the cardiac apex which was unchanged by respiration, as well as a loud, blowing, diastolic murmur along the left sternal border. The abdomen was soft. The liver was not felt. The blood pressure was 100/50. The pulse was regular, and the rate was 100.

From the House of the Good Samaritan, Boston, Massachusetts.
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The corrected sedimentation rate was .28 mm. per minute (normal, .38 mm.), and the leucocyte count was 10,400.

The electrocardiogram, which was similar in all essentials to that reproduced in Fig. 1, showed normal rhythm, a rate of 110, and a P-R interval of 0.13 second.

The diagnosis was rheumatic fever and rheumatic heart disease with mitral and aortic regurgitation.

Ten days after entrance an exacerbation of the rheumatic fever developed; this attack gradually subsided during the next three months. In April, 1938, a severe flare-up of the rheumatic infection began a few days after the onset of an acute upper respiratory infection. A gradual increase in the size of the heart gave evidence of further cardiac involvement. Convalescence was slow, but definite. By the early part of November, 1938, he was free of all signs of active

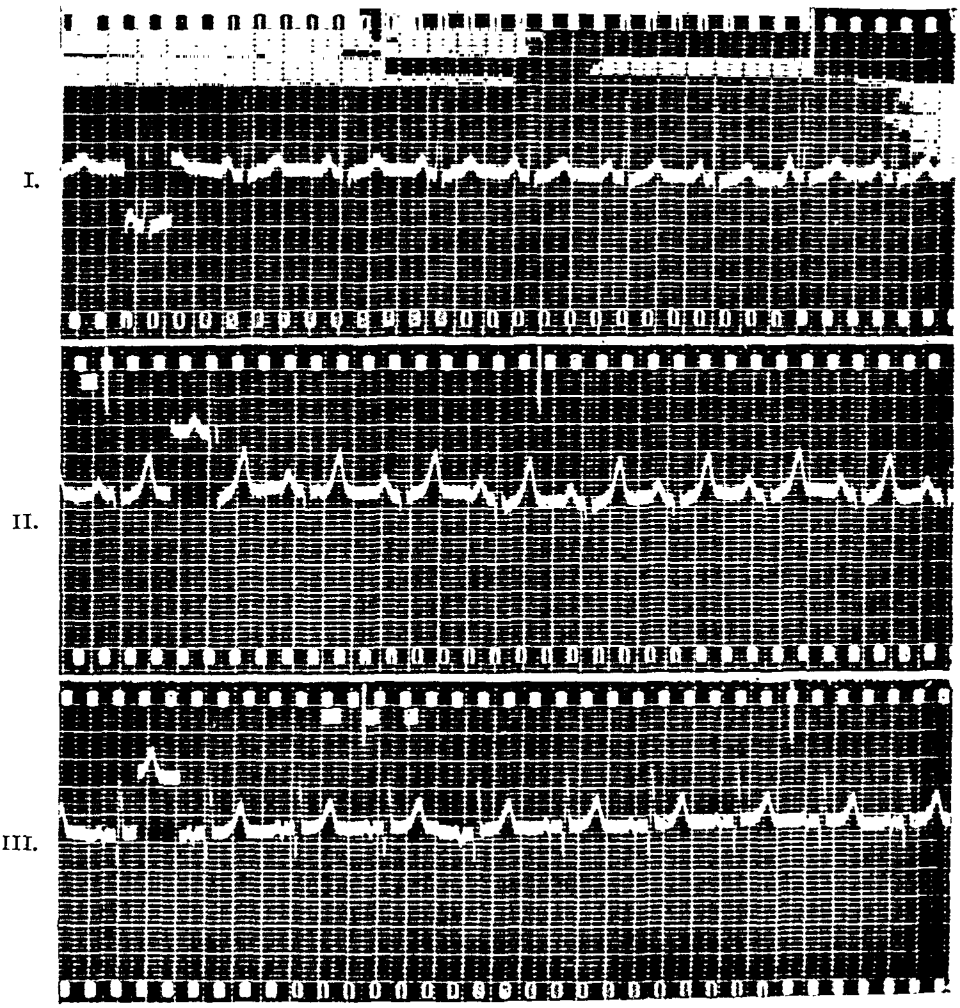
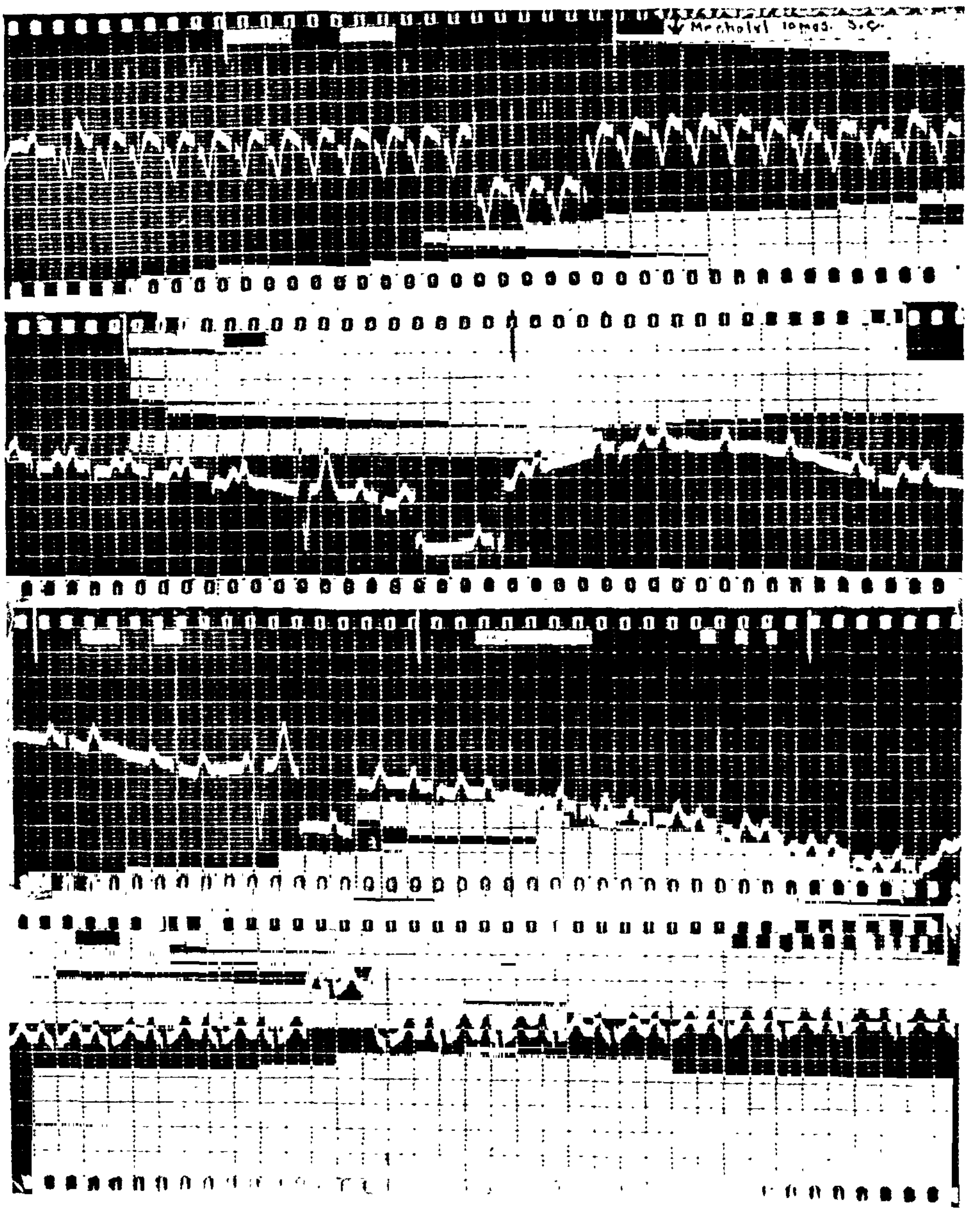


Fig. 1.—Electrocardiogram (April 24, 1939), showing normal rhythm, rate 100, Leads I, II, and III.

infection. However, during the third week of that month rheumatic fever again became manifest. A mitral diastolic murmur appeared, and the intensity of the previously described aortic murmur was increased. Recovery from this, his fourth attack of rheumatic fever while under our observation, was progressing satisfactorily when renewed activity of the infection set in during the first week of May, 1939. This was manifested by fever, anorexia, precordial pain, a more rapid sedimentation rate, and a leucocyte count of 22,000. Congestive failure

ensued in a few days, with enlargement of the liver and slight generalized edema. Aspirin and diuretin (theobromine sodium salicylate) were given, each in doses of 45 grains daily, to control the fever and promote the loss of edema. On the fifth day (May 20, 1939) after the onset of congestive failure, his heart rate rose abruptly to 240 per minute. There was no particular complaint except of pain in the right upper quadrant caused by the tender liver, the edge of which was felt 3 cm. below the level of the previous day.

The electrocardiogram (Fig. 2, Strip 1) showed ectopic auricular tachycardia, with a rate of 240 per minute. Pressure on the carotid sinus and eyeballs did not



1.
2.
3.
4.

Fig. 2.—All Lead II. Strip 1. Ectopic tachycardia of supraventricular type. The exact location of the ectopic focus is probably in the lower part of the auriculoventricular node. Of interest is the isolated, normal, sinus beat shown at the beginning of the strip. Strip 2. Sinoauricular rhythm, with an auricular rate of 130 and progressive auriculoventricular block, finally resulting in a ventricular rate of thirty per minute. The fifth ventricular complex in Strip 2 represents an ectopic ventricular beat. Strip 3. Sinoauricular rhythm, with decreasing auriculoventricular block and return to 1 to 1 auriculoventricular response. Strip 4. Sinoauricular rhythm, rate 130.

after the heart rate. Because of the rapid increase in the existing heart failure the patient's condition was precarious, with the likely prospect of a fatal termination if the tachycardia persisted. It was then decided to use Mecholyl. A single dose of 20 mg. was given subcutaneously. Within three minutes the patient flushed, then blanched, and vomited. The cardiac mechanism began to fluctuate between the tachycardia and regular beating at a rate of 80 per minute. Because of the restlessness of the patient it was impossible to obtain an electrocardiogram during this transition period. Three or four minutes later the heart beat became more irregular, and the ventricular rate fell to 30 per minute (Fig. 2, Strip 2). The patient lost consciousness, and, because we feared a therapeutic catastrophe, $\frac{1}{100}$ of a grain of atropine sulfate was given subcutaneously. Since there was no change during the next two minutes, $\frac{1}{100}$ of a grain of the same drug was injected intravenously. Almost immediately the heart became regular at a rate of 130, with a normal sinus mechanism (Fig. 2, end of Strip 2, Strip 3). Consciousness returned promptly, and after a brief period the patient seemed entirely recovered.

It is of interest that the edge of the liver receded 3 cm. within fifteen minutes after the return to normal rhythm. For the remainder of the day the patient's condition was unchanged. Frequent observation of the heart showed that it was beating regularly at a rate of 130 per minute. However, next morning the tachycardia had returned, with a rate of 220. The electrocardiogram was identical with that shown in Fig. 2, Strip 1.

Mindful of our experience of the previous day, a dose of 5 mg. of Mecholyl was given. In five minutes the patient complained of moderately severe abdominal pain, became nauseated, and vomited. The heart rate then slowed to 70, and the beating was slightly irregular. The excursions of the electrocardiographic string shadow (observed, but not recorded) indicated a high-grade auriculoventricular block. Because of the persistence of troublesome upper abdominal pain, and of the heart block, $\frac{1}{100}$ of a grain of atropine sulfate was given subcutaneously. Three or four minutes later the heart rate became very fast (not recorded) for a few seconds, then the mechanism returned to normal. An electrocardiogram at this time showed normal sinus rhythm, with a rate of 130. To forestall, if possible, further attacks of auricular tachycardia, the patient was digitalized during the next twenty-four hours. There was no return of the ectopic rhythm.

After two days of a relatively satisfactory state, the rheumatic fever increased in severity, with evidence of further myocardial failure. The patient died May 27, 1931, seventeen months after his admission to the House of the Good Samaritan, and three weeks after the beginning of his terminal exacerbation of rheumatic fever.

COMMENT

Paroxysmal auricular tachycardia is generally of short duration and terminates spontaneously. When very rapid or long continued, congestive heart failure may appear, even in persons with otherwise normal hearts. This is caused, as [illegible] indicated, by the progressive shortening of diastole, which results in poor ventricular filling, lowered cardiac output, and venous stasis. The appearance of tachycardia at a rate of 220 per minute in our patient with congestive heart failure caused by rheumatic fever created a critical state. The treatment of such attacks has frequently been unsuccessful, but the advent of acetyl-beta-methylcholine chloride (Mecholyl) provides an additional therapeutic agent which promises to be of value, as in our case, when the

usual measures have failed. By means of this drug, the majority of those who do not respond to the usual measures (pressure over the carotid sinuses and eyeballs, induced vomiting, quinidine, digitalis, etc.) may be relieved. However, it should be emphasized that this drug is a powerful vagus stimulant, and, when given in too large a dose (as in our patient in the initial attempt to restore normal rhythm) it may cause heart block with temporary ventricular standstill. Nevertheless, there are no reported fatalities caused by acetyl-beta-methylcholine chloride, although as much as 300 milligrams have been administered[3] to an adult, with resultant transient cardiac arrest and syncope. Atropine will abolish such an effect almost immediately, and should be prepared in advance for instant use, if necessary. Although the dosage cannot be standardized (Wright[6] has found it necessary to give 100 milligrams in a single injection to a child), children, young people, and those of slight build require less than adults or those of heavy build. In young children it would seem best, in the light of our experience, to use 5 mg. first, increasing the dose in 5 to 10 mg. steps every thirty or forty-five minutes until the attack is stopped or the effects of overdosage appear.

SUMMARY

1. The case of a 5-year-old child who was seriously ill with ectopic auricular tachycardia complicating rheumatic fever, rheumatic heart disease, and congestive failure is described.

2. Normal cardiac rhythm was restored by the use of acetyl-beta-methylcholine chloride (Mecholyl).

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Department of Reviews and Abstracts

Selected Abstracts

Graybiel, Ashton: Diseases of the Heart: A Review of Significant Contributions Made During 1939. Arch. Int. Med. 65: 1053, 1940.

A survey of the literature on cardiovascular disease for the year 1939 reveals much that is of interest and importance. The most notable contributions are in regard to congenital heart disease, essential hypertension and the treatment of subacute bacterial endocarditis. Consequently, these subjects have been reviewed in considerable detail.

This review is the annual one similar to the previous several years. It is an essential part of cardiac literature.

AUTHOR.

Ogden, Eric, Brown, Lewis T., and Page, Ernest W.: The Increased Sensitivity of Arterial Muscle in the Prehypertensive Phase of Experimental Renal Hypertension. Am. J. Physiol. 129: 560, 1940.

Renal hypertensive rabbits were found to be markedly more sensitive to the pressor action of pitressin than they had been before partial constriction of the renal arteries. Similar control operations gave negative results. Hypersensitivity to pitressin was a phenomenon of the prehypertensive or early hypertensive phase. The hypertensive animals also appeared to have an abnormal pressor response to noise and fright. Although the latter stimuli operate through the nervous system, the hypersensitivity to a muscle stimulant, pitressin, leads to the belief that renal hypertension is characterized by a generalized increase in the reactivity of the muscular coat of the arteries and that this in turn may play an essential role in the production of hypertension.

AUTHORS.

Burton, A. C., and Taylor, R. M.: A Study of the Adjustment of Peripheral Vascular Tone to the Requirements of the Regulation of Body Temperature. Am. J. Physiol. 129: 565, 1940.

The rhythmic fluctuations of peripheral vascular tone previously described (Burton, 1939) have been examined under various conditions of heat loss in order to determine how they are modified to maintain an appropriate value for the average peripheral blood flow. The pulsation of the finger volume with each heart beat has been used as an index of general peripheral vascular tone.

Those constrictions which occur in response to external stimuli or are of "psychic" origin may be distinguished from "spontaneous" constrictions by the simultaneous recording of the psycho-galvanic reflex since this, which is an index of sweat gland activity, accompanies only those vasoconstrictions which are of the former type. Otherwise, the intermittent activity in the sympathetic nerves to blood vessels is completely independent of that in the nerves to sweat glands in the palm.

The regularity of the rhythm of spontaneous vasoconstriction has been examined by statistical methods. The interval between constrictions in the

"comfortable" range of environmental temperature is between 30 seconds and 2 minutes with an average interval of 50 to 60 seconds.

As the temperature of the environment is raised, the average interval increases, as more of the longer intervals between constrictions occur.

When the subject is immersed in a well-stirred water bath of constant temperature, the rhythm of vasoconstriction is essentially similar to that found in air. This means that the intermittence of tone cannot be due to a corresponding intermittence of skin temperature. The latter is shown to have so great a thermal lag that such an origin of the intermittence would be very improbable.

The average size of pulsation in the finger, calculated for five-minute periods in the bath experiments, is remarkably constant in spite of wide variation within such a period. The changes in the level of the average size of pulsation and in the average interval between vasoconstrictions, with rising temperature of the water, have been determined. The efficiency of the modification of the rhythmical fluctuations by temperature regulation is demonstrated.

For a given environmental temperature the amplitude of the fluctuations is very similar in normal subjects. In the range of blood flow from 40 to 60 c.c./min./100 c.c. of tissue, it is maximal, with a standard deviation of ±30 per cent.

It is concluded that the reflex adjustment of the blood flow in peripheral vessels, in accordance with the requirements of temperature regulation, is a continuous process which consists in the modification of a vascular tone which is intrinsically rhythmical in character.

AUTHORS.

Jeffers, William A., Lindauer, M. August, Twaddle, Paul H., and Wolferth, Charles C.: Experimental Hypertension in Nephrectomized Parabiotic Rats. Am. J. Med. Sc. **199**: 815, 1940.

Totally nephrectomized rats will survive in parabiosis for two to ninety days following the second nephrectomy. They will show progressive weight loss and azotemia in the last week of life. Terminally hypervolemia and hypertension will usually appear. The probable mechanism of this type of experimental hypertension is discussed.

AUTHORS.

Grimson, K. S., and Shen, T. C. R.: Influence of Benzedrine, N-Methyl-Tetrahydro-Isoquinoline, Histamine, Peptone, and Anaphylactic Shock Upon the Carotid Sinus Vasomotor Reflexes. Arch. internat. de pharmacodyn. et de therap. **62**: 474, 1940.

Phenylaminopropane phosphate (Benzedrine) in small doses produces no alteration of blood pressure or of proprioceptive vasomotor carotid sinus reflexes. Larger doses increase the blood pressure and decrease the vasomotor reflexes by decreasing depressor responses. High doses abolish the vasomotor reflexes of carotid sinus origin.

N-methyl-tetrahydro-isoquinoline may decrease or reverse the hypertensive action of adrenaline without appreciably altering proprioceptive vasomotor reflexes of carotid sinus origin. Larger doses abolish these vasomotor reflexes.

Histamine and peptone in small doses increase the depressor proprioceptive vasomotor carotid sinus reflexes without altering general blood pressure. Larger doses lower blood pressure and greatly decrease the proprioceptive vasopressor and vasodepressor reflexes of carotid sinus origin.

Anaphylactic shock greatly lowers blood pressure and decreases or suppresses proprioceptive vasomotor reflexes of carotid sinus origin.

AUTHORS.

Grimson, K. S., and Shen, T. C. R.: Vasomotor Responses to Adrenaline and to Carotid Sinus Impulses in Normal, Skinned, and Denervated Legs. Arch. internat. de pharmacodyn. et de therap. 63: 95, 1939.

Our studies on the vasomotor responses of normal and skinned limbs, by using the three manometers method of Nolf or by a strohmuhr, show that vasoconstriction and vasodilatation produced by carotid sinus reflexes, direct sympathetic stimulation, and the direct injection of varying doses of adrenaline occur equally well in the normal and in the skinned limb when proper measures are taken to keep the latter warm and moist. These facts thus show that blood vessels of skeletal muscles may also react to vasomotor impulses and adrenaline injections by vasoconstriction and vasodilatation.

AUTHORS.

Shen, T. C. R., and Marri, R.: Further Studies on Cardio-Ventricular Fibrillation. A. Influence of diethylaminoethoxy-2-diphenyl (F. 1262), corynanthine and p. oxyphenyl-ethanol-methyl-amine (sympatol) on the benzol-adrenaline cardio-ventricular fibrillation in the dog. B. The Role of the Hypertensive Action of Adrenaline. Arch. internat. de pharmacodyn. et de therap. 64: 58, 1940.

Simultaneous injection of diethylamino-ethoxy-2-diphenyl (F. 1262) and adrenalin produces an arterial hypotension and prevents the benzol-adrenaline cardioventricular fibrillation. Five to sixty minutes later injection of adrenalin alone produces an arterial hypertension and subsequent death of the benzol-inhaling dog by ventricular fibrillation.

Intravenous injection of corynanthine (0.5 to 2 mg. per kg.) induces a prolonged fall of arterial blood pressure, lasting decrease of the carotid sinus vasomotor reflexes and a decrease of the hypertensive action of adrenalin as well as a protective action upon the benzol-adrenaline cardioventricular fibrillation.

Five to ten mg. of p-oxyphenyl-ethanol-methyl-amine (sympatol) intravenously injected either before or together with adrenalin scarcely protects the benzol-inhaling dogs against ventricular fibrillation.

Intrapericardial injection of 0.2 mg. of adrenalin per kg. into a benzol-inhaling dog produces a progressive rise of arterial blood pressure but provokes no ventricular fibrillation. Intravenous injection of 0.02 Gm. of adrenalin per kg. produces an abrupt elevation of the arterial blood pressure and death by ventricular fibrillation.

The role of adrenalin itself and the arterial hypertension induced by adrenalin in determining the production of the benzol-adrenalin cardioventricular fibrillation is discussed. The characteristic form of the rise of blood pressure which produces the ventricular fibrillation of the chloroform or benzol-adrenalin type is pointed out.

AUTHORS.

Bouckaert, J. J., Grimson, K. S., and Heymans, C.: Increase of Blood Pressure by Perfusion of the Ischaemic Kidneys of Hypertensive Dogs. J. Physiol. 96: 10, 1939.

These experiments show that, under certain experimental conditions, the incorporation of the kidneys of a renal-ischemia hypertensive dog into the circulation of another normal dog will produce an elevation of blood pressure.

In order to be able to induce a sustained high blood pressure, the liberation of this not very active vasopressor renal factor must, however, be associated

with either a primary or a secondary disturbance of the physiologic, under normal conditions very effective, mechanisms of the proprioceptive homoeostatic blood pressure regulation.

AUTHORS.

Adams, W. E., and Escudero, Lucilo: Disturbances in the Circulation and Respiration in Obstruction of the Blood Flow to and From the Heart. Surg. Gynec. and Obst. 70: 744, 1940.

Obstruction of the blood flow through vessels leading to or from the heart was produced in dogs. The resultant variations in cardio-circulatory and respiratory physiology simulated very closely those usually associated with certain clinic conditions. Of the large blood vessels connected with the heart, obstruction of the venae cavae and azygos were by *far the best tolerated. Cardiac activity* remained regular for as long as nine minutes with complete cessation of blood flow to the right heart. Obstruction of the pulmonary artery was tolerated the poorest of that of all the great vessels of the heart, presumably because of the opposite factor, that is, in vena caval obstruction the cardiac muscle is put somewhat at rest whereas in obstruction of the pulmonary artery the right heart burden is greatly increased. The practical application of these findings to clinical problems in thoracic surgery is discussed.

AUTHORS.

Holman, Emile: Hemicardiac Hypertrophy Due to Increased Peripheral Resistance. A Study of Pulmonic and Aortic Stenosis Experimentally Produced. J. Thoracic Surg. 9: 262, 1940.

Aortic stenosis was produced in three very young animals, resulting in marked hypertrophy of the left ventricle without dilatation of the ventricular cavity.

Pulmonic stenosis was produced in two very young animals, resulting in marked hypertrophy of the right ventricle without dilatation of the ventricular cavity.

Hemicardiac hypertrophy under these two conditions is due to an increased resistance, unaccompanied by ventricular dilatation. This is in marked contrast to the cardiac enlargement seen in the presence of a large arteriovenous fistula, which is preponderantly due to a dilatation and only in slightest degree to an hypertrophy. In the presence of a fistula there are a decrease in peripheral resistance at the site of the fistula and an increase in cardiac output, the extent of these changes being dependent upon the size of the fistula.

Cardiac enlargement observed clinically or radiographically, therefore, may be due either to dilatation or to hypertrophy. It is inaccurate to refer to such enlargement as "cardiac hypertrophy" until proved by direct observation of the heart.

AUTHOR.

DeWesselow, O. L. V. S., and Thomson, W. A. R.: A Study of Some Serum Electrolytes in Hypertension. Quart. J. Med. 7: 361, 1939.

The serum of patients suffering from essential and malignant hypertension tends to show a lower level of potassium than that of patients with a normal blood pressure on the same diet; this is especially marked in malignant hypertension.

Low levels of serum-sodium are not infrequent in malignant hypertension. Administration of sodium salts raises the blood pressure of hypertensive sub-

jects, while potassium salts have the opposite effect. These alterations are slight, and the amounts of the salts required to produce them are unlikely to be taken in a freely chosen diet.

Attempts at depletion of the body sodium were without effect on the blood pressure.

AUTHORS.

Thomson, William A. R.: Acetylcholine and Potassium in Relation to Cardiac Function. St. Thomas's Hosp. Rep. 4: 59, 1939.

The effect of acetyl-beta-methylcholine chloride (mecholyl) upon the electrocardiogram and the serum potassium was investigated in seven individuals in whom no abnormality of the cardiovascular system could be detected.

The changes observed in the electrocardiogram consisted of tachycardia, accompanied or followed by sinus irregularity or varying degrees of auriculoventricular heart block. Following the tachycardia, the heart rate usually became considerably slower than the control rate. During the period of tachycardia the height of the T wave was usually diminished and frequently during the subsequent period of slowing T became higher than in the control record.

Following the injection of mecholyl, significant changes in the level of the serum potassium occurred in only two patients, and on both occasions the increase was accompanied by a definite slowing of the heart rate and an increase in the height of the T wave. In the other five patients the effect of the mecholyl had either practically passed off or had not yet begun at the time when blood was withdrawn for the estimation of the potassium.

The bearing of these preliminary observations on the question of the relationship of acetylcholine, potassium, and the digitalis group in their action on the heart is discussed.

AUTHOR.

Cossio, P., Aubone, A. Castro, and Marra, y R. R.: Cardiovascular Tomography. Rev. argent. de cardiol. 6: 209, 1939.

1. Left Auricle and pulmonary veins.

The authors have analyzed the tomographies of normal subjects and of thirty-five patients with mitral disease (mitral stenosis, mitral stenosis with insufficiency, and mitral stenosis with aortic insufficiency). In normal cases the tomographies clearly show the right and left pulmonary veins which can both be followed through the projection of the cardiac shadow. In 70 per cent of the cases with mitral disease the right and left pulmonary veins are also well visualized, as well as the left auricle with both its borders, right and left. The left border is well identified because of the easy visualization of the left pulmonary veins. The trachea and its bifurcation are also made perfectly visible, this making the injection of lipiodol unnecessary for this purpose. In cases in which the right border of the heart shadow is formed by a very dilated left auricle, it is possible to identify through this shadow the right border of the right auricle.

The authors point out that apart from the valuable information obtained by this method in mitral disease, the identification of the pulmonary veins is of importance because: 1) it allows the recognition of their topography in vivo; 2) in doing so, difficulties and errors of interpretation in tomography of the lungs may be avoided; 3) by the identification of the left pulmonary veins the left border of the left auricle is easily recognized.

AUTHORS.

Boyd, Linn J., and Scherf, David: The Electrocardiogram After Mechanical Injury of the Inner Surface of the Heart. Bull. New York Medical College 3: 1, 1940.

In seventeen experiments mechanical irritation (scratching) of the endocardium and of the adjacent myocardium at the apex of the dog heart in situ did not cause a high or low take-off of the final deflection, as seen after similar irritation of the outer layers of the myocardium in the same region. Changes in the form of the T waves and a depression of the S-T segment alone occur. The alterations disappear within a few minutes.

AUTHORS.

Boyd, Linn J., and Scherf, David: The Electrocardiogram in Experimental Pericardial (Epicardial) Injury. Bull. New York Medical College 2: 168, 1940.

Mechanical irritation of the surface of the heart (light blows, pinching, rubbing with sandpaper) at circumscribed areas produces a high take-off of the terminal deflection.

The same alterations develop after concentrated salt solutions and other irritating substances are brushed upon the surface of the heart.

The alterations in the electrocardiogram appear in a few seconds, immediately reach their acme, and decline in a few minutes. The initial deflection remains unaltered. The high take-off is always present in Leads II and III regardless of whether an area on the surface of the left ventricle or the apex of the right is irritated. The alterations of the S-T segment in Lead I upon irritation of the right ventricle consist in a low take-off. The alterations in Lead I after irritation of various areas of the left ventricle do not permit the recognition of any regularity. No electrocardiographic alterations could be obtained from the anterior wall of the right ventricle.

The upward displacement of the S-T segments by a high take-off shortens the S wave in Leads II and III after division of the right bundle branch and can even prevent its appearance. In the presence of a high take-off the typical alterations of the final deflection do not appear after faradic stimulation of the stellate ganglion. However the width of the ventricular complex is markedly diminished.

Isolation of the irritated area from the neighboring tissues diminishes the high take-off considerably or abolishes it.

The alterations of the S-T segment are explained by the admixture of a monophasic current of injury to the electrocardiogram. In addition to the size of the irritated place its contact with the neighboring tissues and apparently also their configuration is decisive for the degree of this admixture. The theory of participation of reflexes or vascular spasm is rejected.

AUTHORS.

Robinson, Samuel C., and Brucer, Marshall: Hypertension, Body Build and Obesity. Am. J. Med. Sc. 199: 819, 1940.

The role of obesity in hypertension is here evaluated by separating obesity from the body build factor with which it is intimately bound.

Obesity is found to be intimately linked to the lateral or broad build type; it occurs infrequently in linear or slender build men and women. Of broad-chested men 37 per cent are heavyweight, whereas only 3 per cent of slender men are heavyweight.

Body build is shown to be closely correlated with hypertension. In any weight group the broad-chested individuals show the highest mean systolic and diastolic pressures, the greatest incidence of hypertension, and the lowest incidence of low blood pressures.

When the build groups are held constant obesity shows an uncertain correlation with hypertension. In those instances where a positive correlation to blood pressure is demonstrated, it is strikingly less significant than the build correlations in nearly every instance.

Obesity shows its greatest correlation to blood pressure in the linear or slender build groups. In the lateral or broad groups no correlation is noted; sometimes there is a reversal of the expected trend.

Therefore, body build is the true genotypic factor which, regardless of his weight, determines in a great measure the predisposition of any individual to hypertension.

The role of obesity in hypertension is found to be small. The current widely accepted role of obesity must be revaluated.

AUTHORS.

Matthews, Edward, and Wood, W. Barry, Jr.: Cardiac Arrhythmia During Cheyne-Stokes Respiration. Bull. Johns Hopkins Hosp. 66: 335, 1940.

Four cases of cardiac failure exhibiting marked arrhythmia of the heart during the phases of Cheyne-Stokes respiration were studied. Simultaneous electrocardiographic and respiratory records were obtained through the entire Cheyne-Stokes cycle in each case. In three of the cases, bradycardia began in late apnea and continued till the latter half of hyperpnea and persisted till late apnea. In one case, in which initial P-R interval was 0.32 second, the bradycardia was due to complete auriculoventricular block. In the other three cases the bradycardia was sinus in type, although in two of the three there were changes in the P waves, suggesting shift in the pacemaker.

Two of the patients had received no digitalis prior to the occurrence of the phenomenon. In the two cases in which it was tested, atropine abolished the arrhythmia without affecting the periodic breathing. Carotid sinus pressure was applied during apnea in two cases and changes in the cardiac mechanism similar to those occurring spontaneously in hyperpnea were produced. In one case, voluntary hyperpnea during a period of apnea provoked a transient alteration in cardiac mechanism. No studies of the arterial blood gases were made.

The reports of previous similar cases are reviewed and possible explanations of the arrhythmia are discussed.

AUTHORS.

Klainer, Max J.: The Prognostic Significance of Right Axis Deviation in Arteriosclerotic and Hypertensive Heart Disease. Am. J. Med. Sc. 199: 795, 1940.

Right axis deviation may occur in hypertensive and arteriosclerotic heart disease, even in the presence of left ventricular hypertrophy.

It is commonly associated with recent attacks of coronary thrombosis and with severe myocardial damage. In thirteen autopsied cases myocardial infarcts were found in ten and diffuse fibrosis in two. Right axis deviation occurs in cases with anterior or posterior infarction singly or in combination.

Of the patients with right axis deviation in whom follow-up studies were made, 83 per cent died within twenty-seven months and 43 per cent of the total series died within one month of its discovery. The occurrence of right axis deviation in patients with hypertensive or arteriosclerotic heart disease without rheumatic and congenital heart disease or cor pulmonale indicates a poor prognosis.

Another mechanism altering the electrical axis of the heart may be widespread necrosis of one ventricle which can completely nullify the effects of hypertrophy of that ventricle.

AUTHOR.

Walzer, Leo: Incidence of Auricular Fibrillation in Mitral Stenosis With Congestive Failure. Ohio State M. J. 36: 281, 1940.

Sixty-nine patients with congestive failure, having mitral stenosis as the predominant cardiac lesion and selected from 309 consecutive patients admitted to Lakeside Hospital with the diagnosis of mitral stenosis, form the basis of this report.

Auricular fibrillation occurs with increasing regularity in the congestive failure of mitral stenosis with increase in age. Seventy-eight per cent of the patients in this series had auricular fibrillation. The chief exception to the concurrence of congestive failure and auricular fibrillation in mitral stenosis was the congestive failure of children and adolescents. Here the congestive failure was a part of the picture of active rheumatic infection.

Auricular fibrillation is to be expected in the congestive failure of mitral stenosis. Its absence warrants an intensive search for evidence of active rheumatic infection. If none is found one should suspect either that mitral stenosis is not present, or, if present, is not the important cardiac lesion.

AUTHOR.

Rosenberg, David H.: Fusion Beats. A Report of a Clinical Instance and an Experimental Study in the Dog. J. Lab. & Clin. Med. 25: 919, 1940.

A clinical case manifesting an ectopic, ventricular, parasystolic rhythm with various degrees of fusion with the normal sinus impulse is recorded. The mechanism involved in the production of fusion beats is demonstrated experimentally in the dog. Attention is directed to the importance of recognizing fusion beats in the electrocardiogram.

AUTHOR.

Gross, Harry: Water Content of the Myocardium in Hypertrophy and Chronic Congestive Failure. J. Lab. & Clin. Med. 25: 899, 1940.

The water content of the myocardium from persons with cardiac hypertrophy and with cardiac hypertrophy with congestive heart failure was determined and compared with that of normal persons used as controls.

The hearts from patients with wasting diseases and from aged persons showed relatively low water contents. Children, on the other hand, showed relatively high myocardial water contents normally and in congestive heart failure.

In cardiac hypertrophy without failure, the water content was not increased. The increase in heart weight in cardiac hypertrophy is due to an intrinsic increase in muscle mass and not to an increased amount of water.

In congestive heart failure the water content of the myocardium was increased due to anasarca which also involved the myocardium. The greatest increase of water was observed in childhood, reaching 82.1 per cent in one instance. Normal figures in the aged patients with wasting diseases may represent actual water retention.

The beneficial effects of diuresis in congestive heart failure may, in part, be due to reduction of excessive myocardial water content, thereby improving cardiac contractility.

AUTHOR.

Luten, Drew, and Wedig, John H.: The Incompatibility Between Congestive Heart Failure and Angina Pectoris. J. Missouri M. A. 37: 96, 1940.

That there is a certain incompatibility between angina pectoris and heart failure is well recognized. It is suggested that this incompatibility may be re-

lated to cardiac tone. Competent study of certain antagonistic factors in these syndromes might possibly throw further light on the precise mechanism involved in the production of angina pectoris.

AUTHORS.

Wright, Irving: Conservative Treatment of Occlusive Arterial Disease. Arch. Surg. 40: 163, 1940.

An attempt has been made to review and evaluate the more important of the methods used in conservative treatment of occlusive peripheral vascular disease, especially arteriosclerosis obliterans and thromboangiitis obliterans. The more general use of the conservative approach definitely affects the statistics on amputations. It should be recognized that it is far better surgery to take meticulous care of small lesions and produce healing than to perform major amputations. In a series of 100 consecutive cases of thromboangiitis obliterans studied since 1931 by Littauer and me, only three major amputations were performed, all on persons who would not stop smoking. Most of the patients have been followed for from two to eight years. The incidence of amputation in this group may be expected to rise with the trauma and other factors incident to the passage of time, but it is extremely doubtful that the former amputation rate of from 40 to 50 per cent will again be observed. For arteriosclerosis obliterans, our figures are not so encouraging. We have not yet compiled statistics on this condition, but we have been impressed by its more hesitant response to therapy. On the other hand, an increasing number of patients who have been advised to submit to amputation are today walking on the condemned leg as a result of conservative therapy. Continued study may result in greater success in this regard. Amputation must be regarded as an admission of defeat, an acknowledgment of the physician's inability to solve the problem with which he is confronted.

It is important that the recent trend in certain quarters toward submitting all patients with vascular disease to the same form of therapy, whether it be use of the pressure suction boot, administration of hypertonic saline solution, or intravenous administration of typhoid vaccine, be discouraged. The problems presented by different diseases and by different patients with the same disease are more frequently unlike than identical. Each should be given individual consideration before the therapeutic regimen is instituted. It is also of vital importance that the conception that peripheral vascular disease is purely local, involving only the extremities, be overcome. Each patient should be submitted to a complete study in order that evidences of vascular damage anywhere in the body may be discovered and proper therapy instituted. For example, it is not yet generally recognized that thromboangiitis obliterans may affect any artery in the body.

AUTHOR.

Homans, John: Lymphedema of the Limbs. Arch. Surg. 40: 232, 1940.

An attempt has been made to sort out and describe the lymphedemas, especially of the lower limbs, which are due to local causes. The elephantiases, that is, those associated with a total disappearance of the lymph vessels, are unexplainable, and, as one might suppose, they are really incurable; that is to say, there is no way of restoring drainage of the tissue fluids. To do away with the swelling, one must remove the tissue in which fluid collects. This need not, as a rule, be done for the thigh. It is enough to reduce the size of the leg below the knee.

None of the other lymphedemas are wholly of lymphatic origin. Those which originate in femoroiliac thrombophlebitis are certainly due in part to involvement

of the larger lymph vessels of the pelvic brim in the perivascular exudate which is so often present in these cases, but venous obstruction (at first) and peripheral vasospasm (later) certainly contribute to the swelling of the limb.

The allergic edemas undoubtedly are going to prove of increasing clinical importance. As yet, it is not known whether such states can become established without definite acute attacks of redness, swelling, and fever. If edemas of this sort can arise quietly, as it were, then the various fungi of the skin must be even more common and have more access to the internal mechanism than is now believed to be the case. Without proposing to be an alarmist, I deprecate the rather general tendency of members of the medical profession to shut their minds to this matter.

The reflex edemas, that is, the rare and picturesque swellings which arise unpredictably from trivial injuries and infections, seem to be related to sympathetic control of the peripheral blood vessels. However, their peculiar mode of origin, especially in trauma to certain nerves (the median and sciatic) should make one careful not to be too certain of their nature, and the hypersensitiveness to touch which is so often associated with them appears to give them a relation to the causalgias. There is much to be learned of the relation of pain, superficial tenderness, and edema, as a complex, to the somatic and sympathetic nervous systems. The reflex pathways concerned with the reflex edemas and causalgia-like states require especial study.

AUTHOR.

deTakáts, Géza, and Reynolds, John T.: Amputation for Peripheral Vascular Disease. Arch. Surg. 40: 253, 1940.

The indications for amputation and the methods and results of amputations done in certain cases of peripheral vascular disease have been discussed. Determination of the proper level of amputation and preparation of the patient are described. Factors decreasing mortality are emphasized. The study was based upon fifty major amputations. Although a mutilating operation, amputation for vascular disease continues to rehabilitate economically handicapped or seriously endangered patients for whom conservative measures are ineffective. The mortality can be reduced to a small, unavoidable percentage, especially by amputation before infection is superimposed on gangrene.

AUTHORS.

Shohet, Allan S., Taub, Samuel J., and Kupersmith, Harry: Studies in Coronary Disease: I. Relation of Coronary Sclerosis to Heart Weight and to Right and Left Ventricular Hypertrophy. Illinois M. J. 77: 240, 1940.

This study is based upon a critical review of 7,970 consecutive autopsies performed at the Cook County Hospital, and is a part of a larger work on the nature and manifestation of coronary disease. Among these, there were 305 cases of proved coronary disease, and of these, 183 cases were discarded because of the presence also of possible noncoronary factors in cardiac hypertrophy, such as hypertension, valvular lesions, syphilis, myocardial inflammatory lesions, pericarditis, thyroid disease, congenital heart disease, anemias, cor pulmonale, and impaired kidney function.

A study of the 122 cases of exclusive coronary disease reveals the unquestionable effect of coronary disease per se on cardiac hypertrophy. The graphs also show a hitherto unrevealed and totally unsuspected reciprocal relationship between the two ventricles and the intensification of the disease of the coronary arteries. It appears that early in the course of the disease both ventricles hypertrophy to an approximately equal degree of their original thickness. However, with an in-

crease in the degree of coronary sclerosis, the left ventricle continues to grow in thickness, while the right ventricle actually appears to lose in thickness until such a time when the sclerosis of the arteries becomes very severe. When this stage is reached, the roles seem to reverse. The left ventricle then thins out somewhat and the right ventricle resumes its progressive hypertrophy. No explanation is offered for this phenomenon.

AUTHORS.

Theis, Frank V., and Freeland, M. R.: Thromboangiitis Obliterans. Treatment With Sodium Tetrathionate and Sodium Thiosulfate. Arch. Surg. 40: 190, 1940.

Intravenous injections of sodium tetrathionate and sodium thiosulfate were usually followed by increased peripheral temperatures, decreased pulse rate, and reduction in blood pressure. These physiologic responses were associated with changes in the oxygen capacity and in the oxygen saturation of the arterial and the venous blood.

These effects were opposite to those that occurred with smoking, which is an important etiological factor in thromboangiitis obliterans. The therapeutic value of sodium thiosulfate and sodium tetrathionate is probably due to the changes produced in the blood and the resulting physiologic responses.

AUTHORS.

Ochsner, Alton, and DeBakey, Michael: Therapy of Phlebothrombosis and Thrombophlebitis. Arch. Surg. 40: 208, 1940.

The therapy of thrombophlebitis is reviewed and is classified into prophylactic, conservative, and radical measures.

The prophylactic measures consist of hydration, mobilization, respiratory stimulation, prevention of increased abdominal tension, application of heat, administration of sodium thiosulfate, hirudinization, and heparinization.

The conservative measures consist of immobilization and elevation of the involved extremity, application of heat, hirudinization, use of compression bandages, and production of vasodilatation.

In the authors' experience, the best therapeutic measure is procaine hydrochloride block of the regional sympathetic nerves. The rationale of this therapeutic measure is discussed, and the excellent results obtained from its employment in twenty-two cases are described. The technique of "sympathetic block" as used by the authors is described briefly and illustrated.

The radical procedures consist of ligation, excision, incision and drainage, and thrombectomy or embolectomy.

AUTHORS.

Harrison, Tinsley R.: Some General Principles in the Bedside Diagnosis of Heart Disease. South. M. J. 33: 308, 1940.

The necessity for a careful analysis of the subjective manifestations of patients with complaints referable to the cardiovascular system has been emphasized. In order to illustrate this, certain features of two symptoms have been considered. Recurrent attacks of weakness have been discussed, and four conditions which are frequently overlooked have been mentioned as common causes of the complaint. These conditions are: (1) sudden change from the recumbent to the upright position; (2) carotid sinus syncope; (3) spontaneous hypoglycemia; and (4) allergic dizziness. The fact that these conditions are usually incorrectly diagnosed unless a very careful history is taken has been emphasized.

Certain aspects of another important symptom, pain in the chest, have also been discussed. It has been pointed out that the diagnosis of angina pectoris is almost entirely dependent upon an accurate history. Certain conditions such as paroxysmal tachycardia, paroxysmal auricular fibrillation, and spontaneous hypoglycemia, which may induce the attacks of angina pectoris in the absence of mental or physical exertion, have been considered. The relation of angina pectoris to chronic pain in the shoulder region has been discussed. The similarity of the pain produced by herniation of the stomach through the esophageal hiatus of the diaphragm to the pain of angina pectoris has been mentioned. Emphasis has been placed on the general principle that a careful and detailed history is usually the most important means of arriving at the correct diagnosis in a patient with a pain in the chest.

AUTHOR.

Wood, Paul: The Action of Digitalis in Heart Failure With Normal Rhythm. Brit. Heart J. 2: 132, 1940.

Digitalis effected demonstrable improvement in eighteen out of twenty cases of congestive heart failure with normal rhythm. This was judged by serial measurements of the venous blood pressure in those with systemic congestion, and of the arm-to-tongue circulation time in those with pulmonary congestion.

Since it has been stated that rheumatic heart disease responds better to digitalis than other etiological types, it is of interest that only one of the present series was rheumatic.

Observations showed that the fall in venous blood pressure following intravenous digoxin was not due to slowing of the heart.

A single observation refuted the view that the beneficial action of digitalis is due to its constricting effect upon the hepatic vein.

AUTHOR.

Weichsel, H. S.: Studies in Peripheral Vascular Diseases. I. Intravenous Calcium in Occlusive Vascular Disease. Ann. Int. Med. **13:** 1150, 1940.

Weichsel reports good results in treating peripheral vascular disease with calcium. The number of patients so treated is not specified. The solution used at first was a 10 per cent calcium gluconate in 10 to 20 c.c. of saline, later 2 grams of calcium chloride in saline. The injections were given intravenously once a week for twelve weeks. The observations are based on thirty recordings of the Tycos recording oscillometer before and after treatment and in addition relief of pain, drop in blood pressure, slowing of pulse, increase in claudication distance, reduction in amount of rest, pain and night cramps, healing of ulcers, and promotion of collateral circulation.

MCGOVERN.

Baker, T. W.: Histaminase in the Treatment of Cold Allergy. J. A. M. A. **114:** 1059, 1940.

This is the report of two cases of cold sensitivity successfully treated with histaminase and gradual desensitization to cold. In each instance the condition had been precipitated by the use of cold water, milk, or handling ice. The use of histaminase for other allergic conditions is suggested.

MCGOVERN.

American Heart Association, Inc.

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THE American Heart Association, sponsor of the first International Health Broadcast, stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

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*Executive Committee.

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Original Communications

THE ESOPHAGEAL PULSE UNDER NORMAL AND ABNORMAL CONDITIONS

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IN THE study of the dynamics of the circulation, graphic methods are indispensable. Although the common methods fail in the case of the left auricle and the descending aorta, the proximity of the esophagus to these structures makes it possible to study them.

The first to mention the existence of a cardiac pulsation in the esophagus was Luciani[1] (1877); ten years later, in 1887, Fredericq[2] made the first thorough study. He described a curve characterized by a negative, auricular, systolic wave and a large negative, ventricular, systolic wave. On the other hand, Rautenberg,[3] in 1907, described an esophageal pulse curve showing positive auricular and ventricular systolic waves. Of those who have investigated this subject subsequently, some agreed with Fredericq (Sarolea,[4] Minkowski,[5] Janowski,[6] Vaquez[7]) and others with Rautenberg (Pace,[8] Clerc,[9] Barie,[10] Bard,[11] Edens,[12] Weitz[13]). As we shall see later, faulty technique, in some cases, and the incompleteness of the study in others, explain these discrepancies.

After the development of electrocardiography, this method, like other graphic methods, was abandoned. Nevertheless, the esophageal pulse is undoubtedly useful in the diagnosis of some obscure valvular diseases, especially in opening a new field for the study of the dynamics of the heart in mitral disease.

METHOD

A brief review of the relations between the esophagus and the heart and great vessels will be helpful in understanding the esophageal pulse.

At the level of the third dorsal vertebra, the esophagus is crossed and compressed by the arch of the aorta. These structures descend from this point together in the posterior mediastinum. The esophagus passes obliquely to the left, and crosses in front of the aorta behind the upper part of the heart. Below this level the esophagus follows the posterior surface of the heart and becomes more and more separated from the aorta, which follows the vertebral column.

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Thus the esophagus is closely related (1) *to the arch of the aorta* at the level of the third dorsal vertebra, (2) *to the upper posterior surface of the left auricle* and the descending aorta at the level of the fifth vertebra, (3) below this, to the inferior posterior surface of the left auricle, and (4) *finally, to the posterior surface of the left ventricle.* These juxtapositions explain the transmission of the pulsations of each of these four portions of the circulatory system to the esophagus.

By placing within the esophagus a sound designed to receive pressure changes (Fig. 1), it is possible to record at these four levels four different curves which we designate from below upward, as follows: (1) the ventricular esophageal pulse, (2) the pure auricular esophageal pulse, (3) the auricular esophageal pulse with arterial impact, and (4) the aortic esophageal pulse.

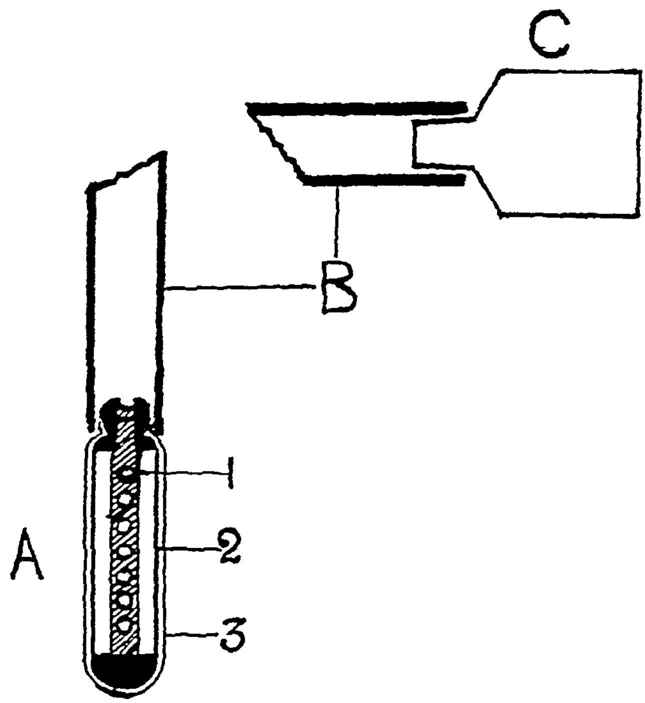

Fig. 1.—*A*, The inferior end of the sound. *1*, Metallic tube, with holes to permit transmission of the pressure changes. *2*, Wire to hold the thin rubber straight. *3*, Rubber membrane. *B*, Rubber sound, connected at its superior end with Frank capsule (*C*).

THE ESOPHAGEAL PULSE

We shall first describe the second, *"the pure auricular esophageal pulse,"* because this is the most complex and because it forms the basis for the other curves.

A. *The pure auricular pulse* is recorded by placing the sound behind the lower half of the left auricle, approximately at the seventh dorsal vertebra. The curve is formed by three positive waves, As, Vs, and VD, and one large negative wave, Vs-D (Figs. 2 and 3).

The As wave is synchronous and coterminous with auricular systole (Fig. 2). It is produced by the contraction of the left auricle. In fact, this cavity becomes round at the beginning of systole and bulges posteriorly, compressing the esophagus. This compression

raises the pressure within and gives the initial positive deflection. With the passage of blood into the ventricle, which decreases the auricular volume, this pressure falls and the curve returns to the baseline.

More often, because the relation between the esophagus and the left auricle at this level is less intimate, the first portion of auricular systole is recorded only partially, or not at all; only the second part of auricular systole, causing a decrease in the auricular volume, changes the intraesophageal pressure, giving an incomplete biphasic, or negative, As wave (Fig. 3).

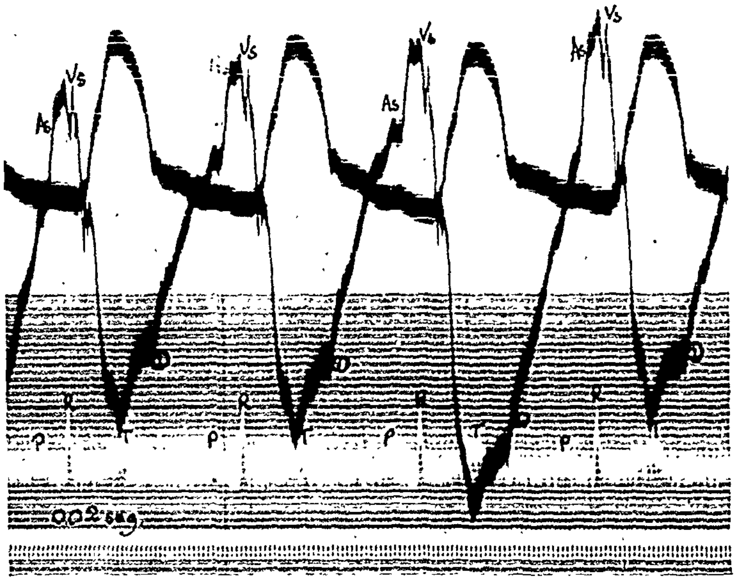

Fig. 2.—From above down are shown, central arterial pulse, pure auricular esophageal pulse, electrocardiogram, and time (0.02 sec.). The esophageal pulse shows positive As wave and large negative systolic wave.

The positive wave Vs marks the beginning of ventricular systole. This wave, of variable amplitude, is characterized by the presence of several oscillations which are the graphic representation of the first heart sound. The closure of the A-V valves and the filling of the auricle during the isometric contraction period may contribute to the production of this wave, but undoubtedly the most important factor is the rapid movement of the heart toward the spine at the beginning of systole.

The fall of the Vs wave is followed by the large, negative Vs-D wave, which occupies the remainder of systole. Point *D*, always very clearly recorded, marks the end of systole, and is characterized by two or three oscillations which represent graphically the second heart sound. This wave, Vs-D, which is typical of this pulse, is produced by displacement of the auricle and inflow of blood from the pulmonary veins during the expulsive period. In effect, during *ventricular systole the*

left auricle is pulled anteriorly and downward toward the apex, separating it from the esophagus. On the other hand, the inflow of blood from the pulmonary veins increases the volume of the left auricle, tending to increase its pressure on the esophagus. The first factor predominates early in systole (when the pull of the ventricle is most rapid), so that the intraesophageal pressure decreases, causing a fall in the curve. Toward the end of systole, however, the inflow factor predominates, and produces the rise of the curve.

Finally, following point *D*, the pure auricular esophageal pulse shows a positive diastolic wave, VD (Fig. 3). This wave is produced by the return of the base of the heart toward the spine at the beginning of diastole, and its later drop is caused by the diminished volume of the auricle as it empties into the ventricle just before auricular systole.

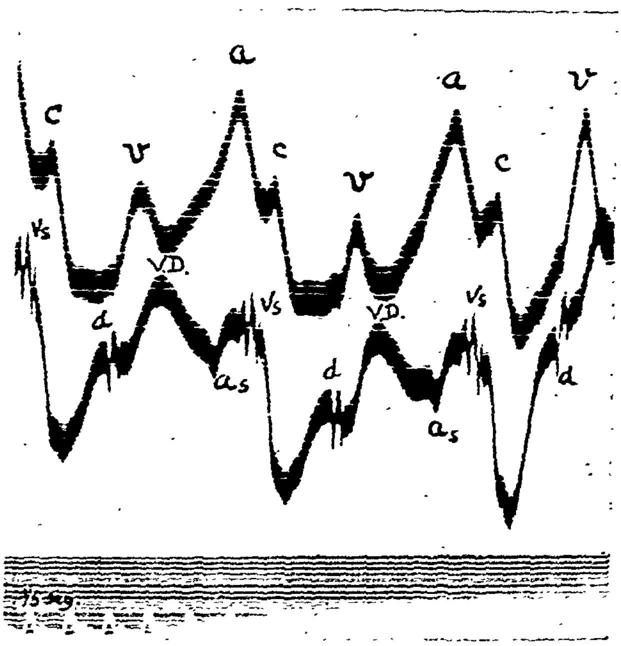

Fig. 3.—Venous pulse, pure auricular esophageal pulse, and time (one-fifth sec.). The esophageal pulse shows negative As wave, negative systolic wave, and positive diastolic wave V.D.

Each of these waves, as we see, is produced by the movement of the left auricle through its own or through ventricular activity. The thoracic inflow and outflow of blood, believed by Mosso to be a factor in changing the intrathoracic and intraesophageal pressure, has no effect on the esophageal pulse. Registration of the esophageal pulse in closed- and open-chest experiments proves this.

The changes in intraesophageal pressure produced by the left auricle extend throughout the length of the esophagus. The As, Vs, and VD waves can be similarly recorded at any level of the esophagus. The waves produced during ventricular systole, however, are changed at other levels by the influence of the descending aorta, transverse aorta, and left ventricle, giving the other three types of esophageal

pulse: (1) the auricular esophageal pulse with arterial impact; (2) the aortic esophageal pulse; and (3) the ventricular esophageal pulse.

B. *The auricular esophageal pulse with arterial impact.*—Behind the upper part of the posterior surface of the heart the esophagus runs between the left auricle and the aorta, which descends behind it. At this level the posterior mediastinum is very narrow. Consequently, the esophagus is compressed by the systolic pulsation of this vessel. The esophageal pulse recorded at this level shows, therefore, instead of the large negative systolic wave, Vs-D, which is produced by the movement of the base of the heart, a large positive wave, I-II, which parallels the curve of the arterial pulse (Fig. 4).

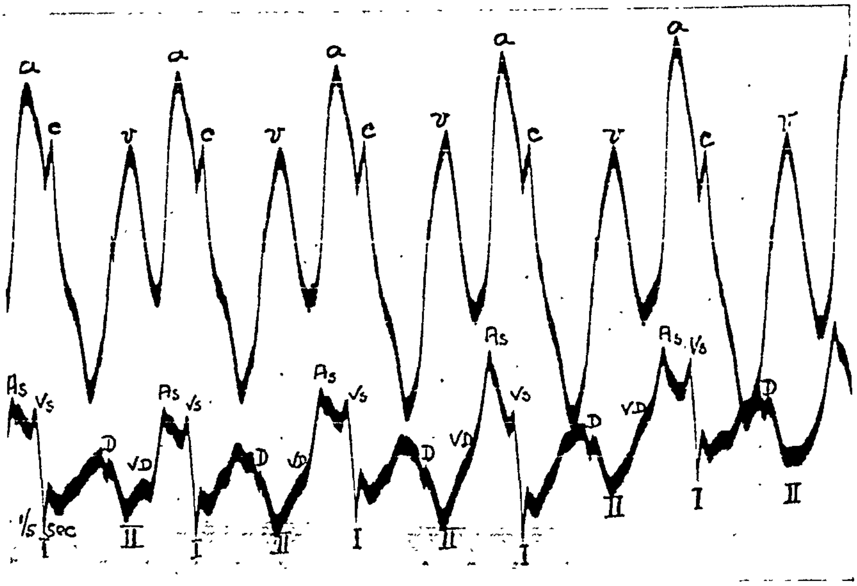

Fig. 4.—Venous pulse, auricular esophageal pulse with arterial impact, and time (one-fifth sec.). The esophageal pulse shows positive As wave and positive systolic wave I, II. The I-II wave is exactly equal to the aortic pulse.

In some patients the posterior mediastinum is deeper, so that the contact between the esophagus and the aorta is less close. In such cases, wave I-II, although always present, may not parallel the aortic pulse so closely (Fig. 5).

The other parts of the curve (As, Vs, and VD waves) are similar to the pure esophageal pulse, since they also are caused by movements of the left auricle. However, because the relation between left auricle and the esophagus at this level is very close, the As wave is completely recorded as a positive wave coterminus with auricular systole, and the Vs and VD waves appear also better differentiated than in the pure auricular esophageal pulse.

C. *The aortic esophageal pulse.*—The esophageal pulse changes again at the level of the aortic knob, becoming what we call the aortic esophageal pulse. It shows, like the other types, the As, Vs, and VD waves (Fig. 6). During systole this curve presents a large negative VS-D

wave which is typical of this pulse. It represents a negative aortic pulse. By recording the central arterial pulse synchronously, it is possible, in fact, to show that the two curves are mirror images.

To explain why the pulsation of the transverse aorta produces a symmetrical, opposite wave in the esophagus, we must remember that the transverse portion of the aorta, in its anteroposterior course, describes an angle which is open to the right. The pulse wave through the aorta, as has been proved by roentgenkymography, straightens out this curve and moves its posterior portion in every systole towards the left, pulling

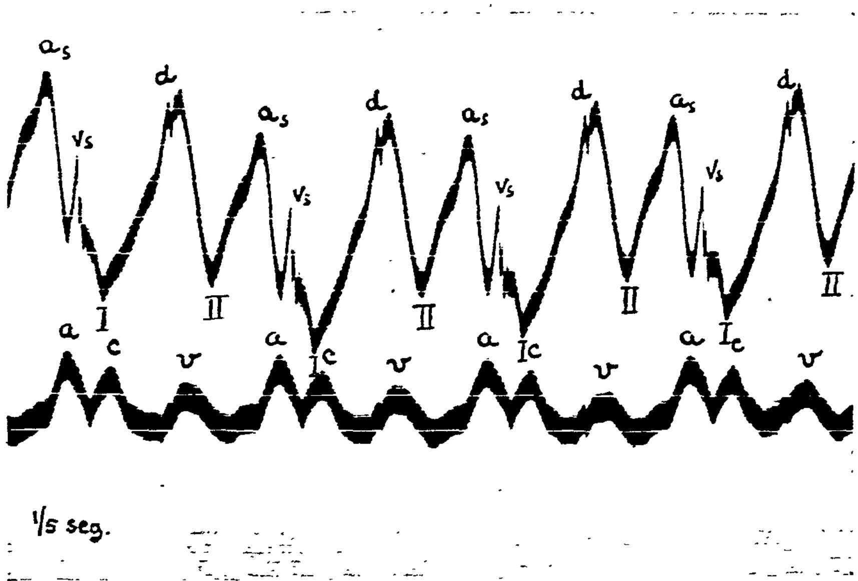

Fig. 5.—Auricular esophageal pulse with arterial impact, venous pulse, and time (one-fifth sec.). The positive I-II wave caused by the aortic impact does not parallel the aortic pulse.

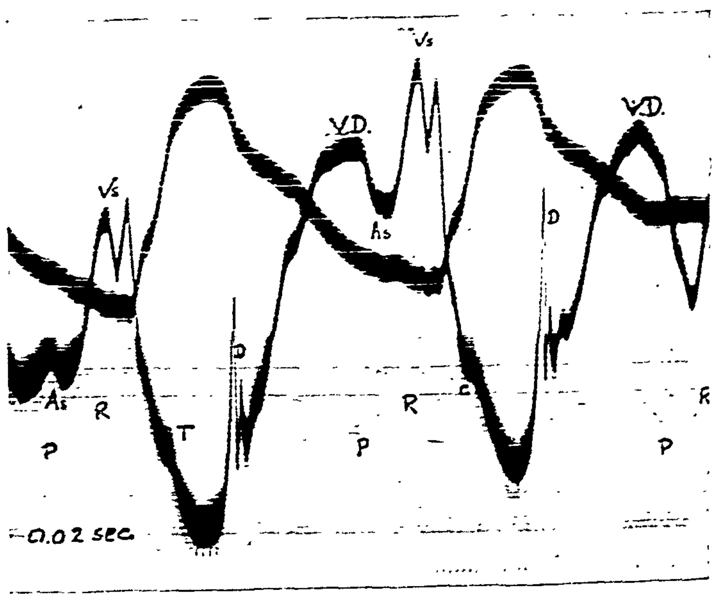

Fig. 6.—Central arterial pulse, aortic esophageal pulse, electrocardiogram, and time (0.02 sec.). The esophageal pulse during systole is a mirror image of the aortic pulse.

the esophagus with it. This shifting of the esophagus, which parallels the pulse of the aorta, decreases the intraesophageal pressure, and, therefore, the pulse curve at this level is the mirror image of the aortic pulse.

D. *The ventricular esophageal pulse.*—Finally, we have to consider what we call the ventricular esophageal pulse. This curve, which is recorded in the lower portion of the esophagus, is similar to the pure auricular esophageal pulse. As we said before, it is produced by the propagation of the changes of pressure produced by the left auricle. Nevertheless, the proximity of the ventricle makes the oscillations caused by the first and second sounds appear much more pronounced at this level than at any other. This gives the curve a typical aspect which permits its differentiation from the other types (Fig. 7).

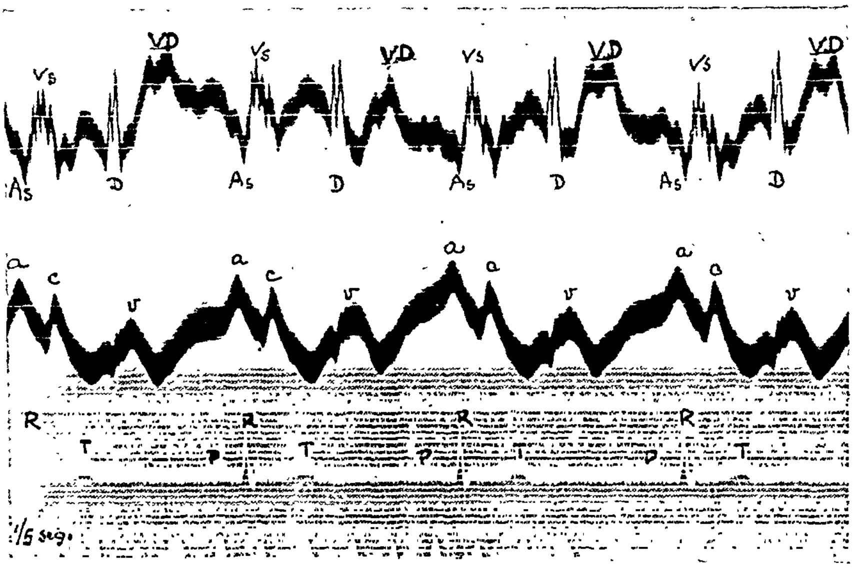

Fig. 7.—Ventricular esophageal pulse, venous pulse, electrocardiogram, and time (one-fifth sec.). The esophageal pulse shows the great amplitude of the oscillations caused by the heart sounds.

In summary, the normal esophageal pulse may be of four different types (Fig. 8)—the ventricular esophageal pulse, the pure auricular esophageal pulse, the auricular esophageal pulse with arterial impact, and the aortic esophageal pulse. The auricular pulse, the most important from the clinical point of view, varies, depending upon whether it is taken behind the upper or lower part of the left auricle. Behind the lower part of the left auricle, because the mediastinum is wider, the esophageal pulse is caused entirely by the movements of the left auricle, and therefore always shows a negative systolic wave. Behind the upper part of the left auricle, because the mediastinum is very narrow, the esophagus has a closer relation to the left auricle, and at the same time enters in contact with the descending aorta. Consequently, at this level the curve always shows, during systole, a positive wave caused by the pulsation of the aorta.

This difference explains the discrepancies among the results of other investigators who have worked on this subject. It shows, too, the necessity of knowing all of the different types of esophageal pulse in order to get any useful information in clinical or experimental studies.

ESOPHAGEAL PULSE IN PATHOLOGIC CONDITIONS

The esophageal pulse has been used in the diagnosis of the arrhythmias and valvular diseases which affect the function of the left auricle. Electrocardiography has supplanted it in the former instance, but it still remains useful in diagnosing what would otherwise be obscure mitral lesions or dilatations of the descending aorta. Experimentally, by permitting an evaluation of the degree of mitral regurgitation and the strength of the left auricular contraction, this method opens a new field for the study of circulatory dynamics in mitral disease.

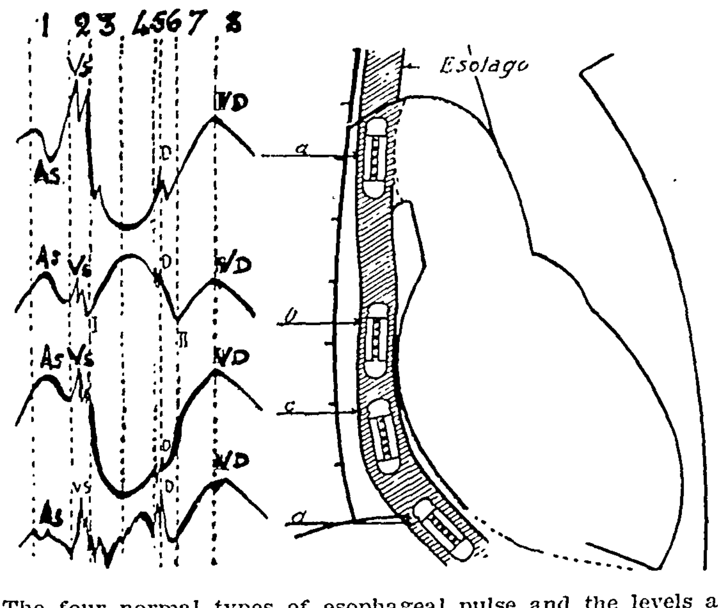

Fig. 8.—The four normal types of esophageal pulse and the levels at which they occur. *1*, auricular systole; *2*, isometric contraction phase; *3*, maximum ejection phase; *4*, reduced ejection phase; *5*, protodiastolic interval; *6*, isometric relaxation phase; *7*, rapid inflow; *8*, diastasis.

1. *Esophageal pulse in mitral disease.*—Even though, anatomically, in most of the cases mitral stenosis and regurgitation are present together, we shall examine separately the esophageal pulse from patients who have clinically pure stenosis, or clinically pure regurgitation, of the mitral valve.

a. *Esophageal pulse in mitral regurgitation.*—The curve of the esophageal pulse in cases of mitral regurgitation begins, as in the normal, with the As wave, which is produced by auricular systole (Fig. 9). Generally, this wave is positive and large. The VS wave, which follows, indicating the beginning of ventricular systole, is continued with, or followed by, a large positive wave, I. This wave occupies all or part

of ventricular systole; it is constant and characteristic of mitral regurgitation. After the end of systole, marked by point *D*, the curve, unlike the normal, shows a sharp drop which coincides with the isometric relaxation phase. Following this point, the curve does not differ from the normal. The I wave and the drop at the beginning of diastole in the esophageal pulse, therefore, are diagnostic of mitral regurgitation.

The constant presence of the I wave, and the moment of its appearance, plus the anatomic position of the heart, lead us to say that this wave is produced by regurgitation of blood through the mitral orifice. The varying duration of this wave in different cases depends on three factors: the tonus of the auricular muscle, the degree of filling of the auricle, and the severity of the valvular defect—factors which influence the amount of regurgitation. In cases of marked mitral regurgitation, with auricular fibrillation and a rapid ventricular rate, in which there is a ready influx of blood to the auricle, the I wave is high and parallels the intraventricular pressure; on the contrary, when the auricle has good tonus and there is a less marked valvular defect, the regurgitation appears only at the moment of higher intraventricular pressure. The esophageal pulse shows, then, an I wave which is recorded following the Vs wave and occupies only the maximum expulsion phase.

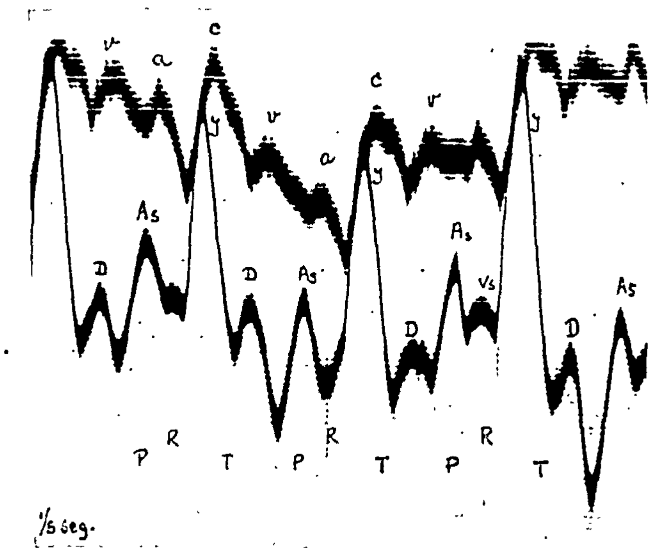

Fig. 9.—Venous pulse, esophageal pulse in mitral regurgitation, electrocardiogram, and time (one-fifth sec.). The esophageal pulse shows the high positive I wave produced by the regurgitation, and the sharp drop that follows point *D* produced by the rapid emptying of the auricle immediately after the beginning of diastole.

The fall of the esophageal pulse curve in these patients during the period of isometric relaxation is also characteristic. The mechanism of its production is as follows: The mitral regurgitation equalizes

the pressure within the auricle and ventricle during systole; therefore, the condition for the existence of a phase of isometric relaxation disappears, and the blood passes, as a consequence, from the auricle into the ventricle at the very beginning of diastole. The emptying of the auricle, which is overdistended by the regurgitant flow, produces a diminution of its volume and a decrease in the intraesophageal pressure, resulting in the drop of the pulse.

b. *Esophageal pulse in mitral stenosis.*—In clinically pure mitral stenosis, with a crescendo presystolic murmur, the esophageal pulse is also typical (Fig. 10). The curve, taken with the sound placed behind the left auricle, shows a biphasic As wave, which begins with auricular systole. This wave is formed by a small rise, followed by a very sharp and deep negative phase which ends with the beginning of ventricular systole. The ventricular systole begins, as normally, with the Vs rise, which is followed by a sharp, short, positive I wave. This latter wave varies in amplitude and duration. It may continue or follow the Vs wave, giving a large summation or two smaller waves. The remainder of the curve, generally, is like the normal. However, in some records of patients with old mitral stenosis there appears, after point *D* (second sound), a new group of oscillations which are caused by the opening snap of the sclerotic valve.

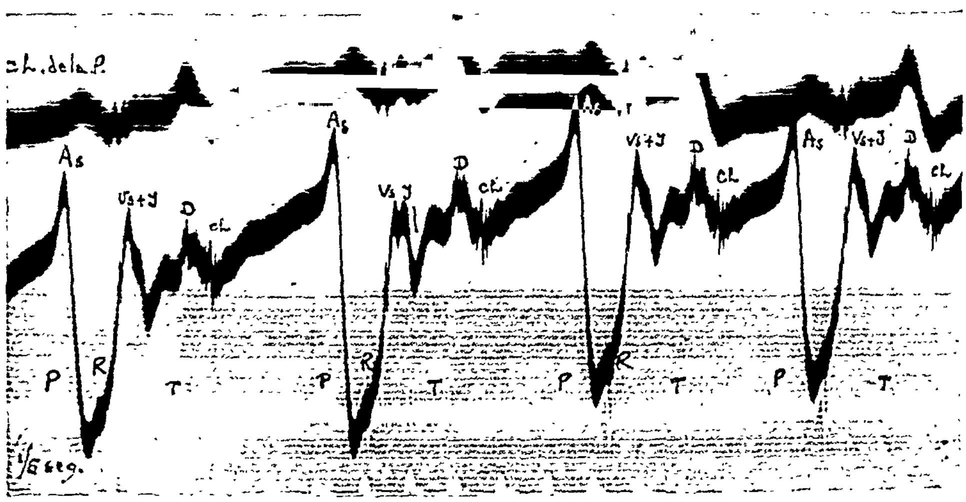

Fig. 10.—Apical pulsation, esophageal pulse in mitral stenosis, electrocardiogram, and time (one-fifth sec.). The esophageal pulse shows the larger As wave.

In discussing the normal esophageal pulse it was said that the fall of the As wave is produced by the decrease in the volume of the left auricle which occurs with expulsion of blood into the ventricle. The large amplitude of this wave in mitral stenosis with a crescendo presystolic murmur indicates that the amount of blood passing to the ventricle during auricular systole is increased. Judging from these facts, auricular systole must be, in some cases of mitral stenosis, indispensable in

order to maintain the filling of the ventricle, and, as a consequence, to maintain the cardiac output and sufficiency of the heart.

The positive I wave, which is similar to, but smaller than, that which occurs in mitral regurgitation, is caused by regurgitation of blood through the mitral valve. Since this wave has appeared in all cases of this type, study of the esophageal pulse has tended to substantiate the belief that mitral stenosis is never "pure."

2. *Esophageal pulse in aneurysm of the descending aorta.*—The descending aorta, because of its position deep in the posterior mediastinum, is sometimes difficult to visualize, so that it may be hard, even with the help of the roentgenologist, to differentiate between a tumor and an aneurysm deeply placed behind the lower part of the heart. In cases of this sort, an esophageal pulse tracing may enable one to make the correct diagnosis. As we have said before, because the mediastinum in the lowest part of the thorax is wide, the esophagus and the aorta are normally separated. Therefore, normally, the pulse from the lower part of the esophagus does not show any effect produced by the aortic pulse, but when there is a dilatation of the descending aorta at this level, this vessel is able to compress the esophagus with each pulsation, and this gives a typical arterial impact in the esophageal pulse (Fig. 11).

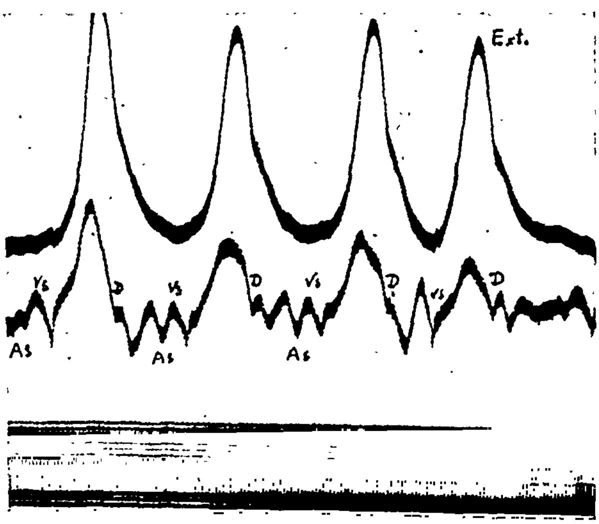

Fig. 11.—Central arterial pulse, esophageal pulse in retrocardiac aneurysm of the descending aorta, and time (0.02 sec.). The esophageal pulse shows a positive systolic wave cause by pulsation of the aneurysm.

The esophageal pulse in such cases bears an aspect similar to the auricular esophageal pulse with arterial impact, which, as we said before, only appears normally behind the upper part of the posterior surface of the heart. The presence, therefore, of this type of pulse in the lower part of the thoracic esophagus is a very important sign of dilatation of the descending aorta.

SUMMARY AND CONCLUSIONS

The normal esophageal pulse varies with the level at which the curve is taken.

Normally there are four types of esophageal pulse: (1) the aortic esophageal pulse, (2) the auricular esophageal pulse with arterial impact, (3) the pure auricular esophageal pulse, and (4) the ventricular esophageal pulse.

In cases of mitral stenosis, mitral regurgitation, and aneurysm of the descending aorta the esophageal pulse shows changes which are typical of these lesions.

Study of esophageal pulses has shown that the duration of the diastolic phases of the left ventricle in mitral regurgitation is abnormal.

The amplitude of the contraction of the auricle in mitral stenosis, as shown by the esophageal pulse, suggests that in this disease the amount of filling of the ventricle which results from auricular systole is increased.

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PRODROMAL PAIN IN CORONARY OCCLUSION

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INTRODUCTION

Coronary occlusion occurs in some patients without any warning, whereas in others it is preceded for varying periods by attacks of cardiac pain which can be classified into two distinct groups, namely, angina of effort and angina at rest. The former has been carefully studied, diagnostic criteria have been established, and its significance is fairly well understood. In contradistinction, the angina which occurs at rest, other than in association with myocardial infarction, has received little attention in medical literature.[1, 2] Our discussion concerns the cardiac pain which occurs without exertion, but does not include that which is associated with extracardiac conditions, such as aortic aneurysm and paroxysmal hypertension, or with changes in the heart rhythm, such as paroxysmal tachycardia. In the cases reported,[1, 2] and in those to be described, the cardiac pain occurred spontaneously, without obvious cause, and always preceded the definite manifestations of coronary occlusion. The attacks, therefore, have been called "prodromal," "premonitory," or "preliminary."

Because it is impossible to ascertain exactly when coronary occlusion is initiated, it is possible that the manifestations which are called "prodromal" are in some instances those of the actual occlusion. The term "coronary occlusion," in this discussion, however, is applied only to those attacks during which the patient exhibited typical symptoms, signs, and electrocardiographic abnormalities which persisted, rather than transient manifestations characterized chiefly by pain.

There is some tendency to discount the significance of atypical thoracic pain because of the definite danger of attracting a neurotic person's attention to his heart. It is important, however, that prodromal pain be recognized, for a fairly large percentage of patients who subsequently develop coronary occlusion have definite warning symptoms, and, in the future, treatment which will prevent thrombus formation may be discovered. The study of the features of prodromal attacks may, in any event, contribute to our understanding of the pathogenesis of coronary occlusion.

Histories obtained from thirty-two patients revealed that twelve had experienced spontaneous, painful attacks for varying periods before the onset of the severe manifestations which were recognized

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as those of coronary occlusion. Nine of the thirty-two patients died, but, with three exceptions, it was possible to obtain a detailed and accurate history. A brief résumé, with particular reference to pain, of the histories of the twelve patients whose attacks were considered to be "prodromal" is given, together with a more detailed description of the clinical and necropsy observations in the one case in the "prodromal" group in which death occurred. In this case, the mechanism of the production of the "prodromal" pain is discussed in the light of the pathologic anatomy.

REPORT OF CASES

CASE 1.—G. W., a 40-year-old white architect, was in good health except for the symptoms of peptic ulcer, which were controlled by dietary treatment. Four days before his coronary occlusion, the patient developed a severe aching pain, together with marked weakness, in the entire left upper extremity. The pain and weakness were so severe that he carried his left hand in his coat pocket in order to support and immobilize the arm. He continued to work. The discomfort was continuous, without exacerbations, and was unaffected by exertion. There were no other symptoms.

While seated at his desk, four days after the onset of pain and weakness in the left arm, forearm, and hand, the patient suddenly experienced severe retrosternal pain which radiated across his anterior chest between the midclavicular lines. There were moderate dyspnea, profuse generalized sweating, and moderate prostration. He was taken to a hospital, where "coronary thrombosis" was diagnosed.

An electrocardiogram which was taken sixteen days after the onset of the acute symptoms was of the Q_3 T_3 type, indicating infarction of the posterior wall.

CASE 2.—F. T., a 48-year-old white carpenter, was found to have a "blood pressure of 188" about ten months prior to his coronary occlusion. This was discovered in the course of a routine physical examination; the patient had had no symptoms attributable to hypertension. One week before his major attack, he was awakened from a sound sleep by an "aching" pain in both shoulders, more marked in the left. The "ache" subsided in ten or fifteen minutes, and the patient fell asleep. The next morning, on getting out of bed, he noted some "soreness" in both shoulders, again more marked on the left, but this disappeared in one or two hours. There was no accompanying dyspnea, sweating, or discomfort in the chest or abdomen. This chain of events was repeated each night for seven successive nights.

On the eighth day, while at work, the patient suddenly experienced severe, retrosternal, "squeezing" pain that immediately radiated laterally as far as the parasternal lines between the fourth and sixth intercostal spaces. There was a recurrence of the "ache" in both shoulders, with extension down the left arm as far as the wrist. Dyspnea, sweating, and prostration were marked, and, thirty minutes after the onset of the attack, syncope of unknown duration occurred, at which time the blood pressure was found to be "120 mm. Hg."

The patient was admitted to the hospital five hours after the onset of his severe attack. The diagnosis of coronary occlusion was confirmed by serial electrocardiograms which did not show any definite localizing pattern.

CASE 3.—G. C., a 48-year-old desk worker, was in good health until 8 A.M. of the day preceding his acute occlusion. At that time, while sitting at his desk, he

noted a slight ''ache'' over the anterior portion of the chest between the midsternum and the left anterior axillary line, extending from the fourth to the seventh intercostal spaces. There was slight dyspnea. The symptoms were so moderate, however, that the patient continued to work, and, by 4 o'clock the same afternoon, he felt perfectly well. In the evening he did some light carpentry about his house, and he slept well that night.

The next day, at 8 A.M., while at his desk, he noted a recurrence of his ''ache'' and dyspnea. The ''ache'' was identical in character and location with that of the preceding attack, but was somewhat more severe, as was his dyspnea. He continued working, however, and at noon did some shopping. He ate no lunch. The patient returned to his desk about 1 P.M.

At 2 P.M. there was a sudden acute exacerbation of his pain and dyspnea. In addition, there were profuse generalized sweating and moderate prostration. The character of the pain was the same as that of the preceding day and the morning attack, except that it was more severe.

The patient was admitted to the hospital three hours after the onset of his acute pain. The diagnosis of coronary occlusion was confirmed by the electrocardiograms, which were of the Q_3 T_3 type.

CASE 4.—R. G., a 45-year-old white carpenter, was in excellent health until April 14, 1939, ten days prior to his major attack. On that day, while working, the patient developed a persistent ''dull ache'' between the parasternal lines from the second to the fourth intercostal spaces. There were slight dyspnea and generalized sweating. The ache lasted from one to two hours.

In the succeeding four days the patient had two similar attacks, neither of which lasted more than two hours.

On April 23, 1939, immediately following a light lunch, the patient had his fourth attack. The pain was identical in character and location with that of the preceding attacks, but was more intense. Dyspnea and sweating were more marked than previously. This attack lasted five hours and subsided spontaneously. The following morning, while at work, the patient had another attack which was even more distressing than that of the day before.

He was hospitalized four hours after the onset of this acute attack, at which time the electrocardiogram showed marked displacement of the RS-T segment ($S\text{-}T_1$ and S-T in Lead IV F were depressed 2 mm. and 8 mm., respectively, and $S\text{-}T_2$ and $S\text{-}T_3$ were elevated 4.5 mm. and 6.5 mm., respectively) which later retrogressed as the patient recovered.

CASE 5.—I. W., a 47-year-old white building guard, developed persistent, ''toothache-like'' pain in the left elbow two weeks before his major attack. The pain was severe enough to keep him awake part of each night and was present during his waking hours.

About six days after the onset of this pain, while walking along the street, the patient developed marked, retrosternal, ''squeezing'' pain, dyspnea, and extreme generalized weakness. He managed to walk home, however, and called a physician, who administered a hypodermic which relieved him greatly. Within three hours the attack had completely subsided, and the patient fell asleep. On awakening the next morning he felt well.

One week later, while sitting in the physician's office waiting to be examined, there was a sudden recurrence of the chest pain, but this time it was much more severe than before. In addition, the pain involved the left arm and elbow, and dyspnea and prostration were marked. The patient was brought to the hospital that afternoon. The following day a pericardial rub was audible over the lower

end of the sternum. Serial electrocardiograms during this attack showed changes of the Q_1 T_1 type which were indicative of myocardial infarction.

CASE 6.—F. P., a 46-year-old white office worker, was in good health until four months prior to his acute occlusion. At that time, while *at rest, the patient* developed an attack characterized by "swelling" inside his neck, and numbness, tingling, and marked weakness of both upper extremities. There was slight dyspnea. The attack subsided in sixty minutes, but was succeeded by a sense of "constriction" over the anterior portion of the chest, between the nipples from the third to the sixth intercostal spaces. There was slight "heaviness" over the anterior portion of the chest. These symptoms disappeared in about sixty minutes, and he felt perfectly well.

One month later, while working at his desk, the patient had a second attack which was identical with the first. A physician who saw him advised twenty-four hours' rest in bed.

Thereafter, the attacks recurred about every three days. They occurred most often in the morning, frequently when he was shaving. *Amyl nitrite shortened the* attacks and ameliorated the pain, but could not prevent nor completely abolish it. *The patient had more than one hundred attacks of the character described above in a period of four months.* They bore no constant relation to exercise or eating.

On August 24, three days before admission, the patient experienced an attack while shaving. The chest, neck, shoulder, and arms were involved, and the pain was severe. Dyspnea and weakness were marked. The patient came to the Outpatient Department and an electrocardiogram was made; it showed a Q_3 of 2.5 mm., inversion of T_2 and T_3, slight elevation of S-T_2 and S-T_3, and an isoelectric S-T_1 and S-T in Lead IV F. All this was interpreted as evidence of coronary occlusion, and hospitalization was advised, but refused. The patient had an apprehensive night because of pain and orthopnea.

He stayed at home for the next three days because of weakness. At 5:30 P.M., August 27, another attack, which was identical with all of his previous ones, occurred. Dyspnea, "swelling" in the neck, and tingling of the arms were very severe, but soon subsided, only to be replaced, as on previous occasions, by chest "constriction" and precordial oppression. The patient was brought to the hospital, where the attack subsided, without medication (morphine was refused), in about twelve hours, but there were frequent, short recurrences in the next three days.

An electrocardiogram which was taken August 31 differed somewhat from the preceding tracing, in that the RS-T deviations were more marked, and the QRS complex in Lead III was more negative.

CASE 7.—H. D. M., a 60-year-old lawyer, felt perfectly well until 11 A.M., July 21. At that time, while at his desk, he developed a "burning, crushing" pain which extended between the two midclavicular lines, from the fourth to the sixth intercostal spaces. It began insidiously, but within fifteen minutes was severe enough to cause the patient to stop working. The pain began to subside within thirty minutes, but did not completely disappear until 6 P.M. that day. There was no accompanying dyspnea, sweating, or faintness.

The following two days were uneventful, and, on the evening of July 23, physical examination revealed a blood pressure of "164," with a "normal pulse." The patient felt well until the evening of July 28. At that time, while sitting at home, the "burning, crushing" pain which he had experienced six days previously recurred. Again, it began in an insidious manner, but within sixty minutes was quite severe. In addition, at the height of the attack, a "gnawing" pain developed in both shoulders and arms, extending to the elbows. There were concomitant "numbness and tingling" of the fingers of both hands. The patient went to bed, and within two hours the pain had decreased so much that he fell asleep without medication. The

next morning (July 29) he awakened feeling weak, but otherwise normal. He came to the hospital for an electrocardiogram (Fig. 1*B*), which was normal except for left axis deviation and a diphasic T wave in Lead IV F.

The patient rested at home for the next three days, and, on August 1, returned to work. That evening he again visited his physician, who found the patient's blood pressure "somewhat lower," but no other abnormality was noted.

The next morning, on the way to work (9 A.M.), the pain recurred, and within an hour became extremely severe. It was identical in character, location, and radiation with that of his preceding attacks. Prostration was moderately marked, and the patient felt that he was about to die. The pain gradually diminished over the course of the three days, but there were frequent flare-ups in its intensity during that period. On August 5 he was admitted to the hospital. An electrocardiogram (Fig. 1*A*), which was taken August 6, showed changes indicating acute myocardial damage.

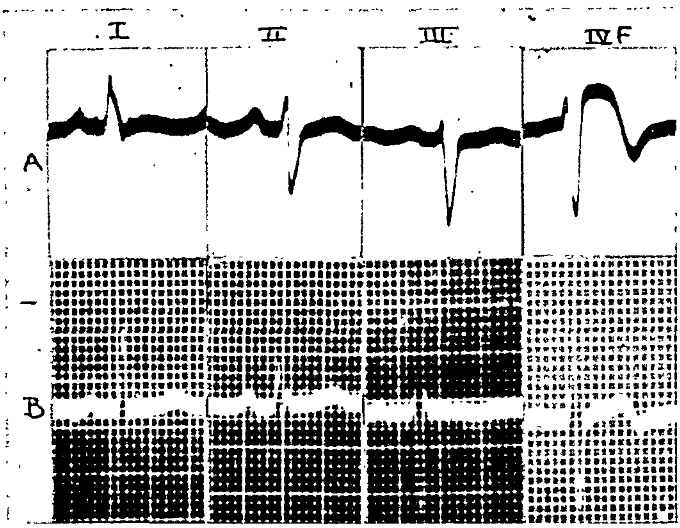

Fig. 1.—Case 7. *A*, Electrocardiogram on August 6, four days after development of coronary occlusion.

B, Electrocardiogram on July 29, eight days after onset of prodromal attacks, and one day after second prodromal attack.

CASE 8.—H. E. S., a 44-year-old white accountant, felt perfectly well until August, 1937. At that time he began to experience attacks of "constricting" pain which was located between the midclavicular lines in the fourth and fifth intercostal spaces, and was associated with a sense of pressure over the anterior chest wall. These attacks would come on suddenly at full intensity, and last two or three minutes. The pain was of only moderate severity. There was no sweating, nausea, or vomiting associated with the attacks, and they bore no relation to meals or exertion. No relief was obtained by the use of sodium bicarbonate. In October, 1937, because of the recurring attacks, the patient came to the Outpatient Department, where physical examination and the electrocardiogram showed nothing abnormal (Fig. 2*A*). *He had had about ten attacks.*

The attacks became progressively more frequent, more severe, and of longer duration, until June, 1938. *Between August, 1937, and June, 1938, the patient had over thirty attacks of pain as described, all of which were associated with moderate dyspnea.*

On June 23, 1938, after playing three innings of softball with absolutely no discomfort, the patient relinquished his position on the field to allow another player to get into the game. He was feeling very well, but, about five minutes later, while

watching the game, he was suddenly seized by a very severe paroxysm of pain which was similar in character and location to that experienced in his previous attacks. The pain was intense, and the patient noted extreme weakness of his left arm and forearm. He managed to drive twelve miles to his home, but had to make several stops because of the severity of the pain in his chest and arm. In thirty minutes the pain began to decrease, and the patient was able to fall asleep. On awakening *the next morning he had no discomfort, but was weak.*

Between June 23 and June 30 the patient felt well, but, on June 30, he had an attack of extreme severity. The pain in his chest and both arms, as well as his dyspnea, was *severe. The patient collapsed and was admitted to a hospital. The pain persisted* in a severe form for twenty-four hours and then slowly subsided over the course of three days. An electrocardiogram which was taken July 22 showed changes of the Q_1 T_1 type which suggested *myocardial infarction (Fig. 2B).*

CASE 9.—J. H., a 60-year-old white clerk, was in excellent health until June 15. About 8:30 A.M., while walking to work, he suddenly developed a "dull lump" at the base of his neck and "inside" the upper part of his chest. There was concomitant "aching" of the left arm as far as the elbow. Moderate dyspnea and slight sweating were noted. The patient stopped at a neighbor's house and took some bicarbonate of soda. Rapid relief of all symptoms followed. The attack lasted about fifteen minutes.

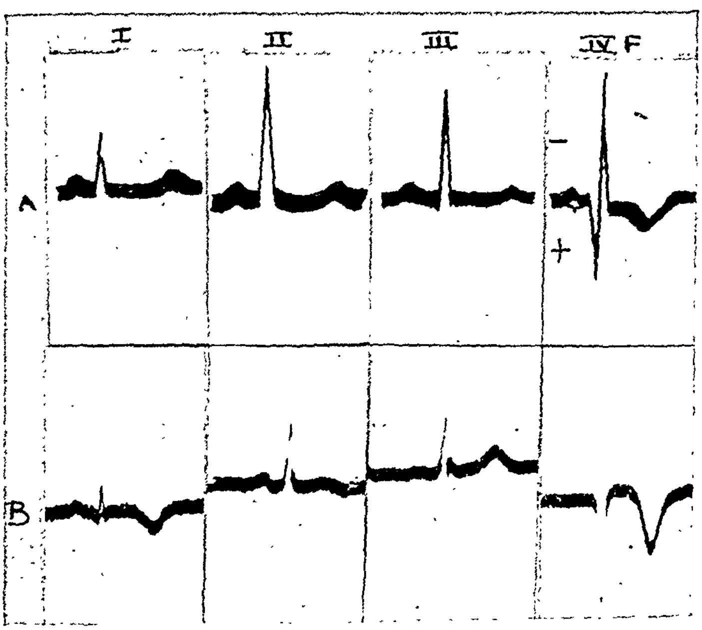

Fig. 2.—Case 8. *A*, Electrocardiogram on Oct. 28, 1937, two months after onset of prodromal pains. The patient had had ten attacks before this tracing was taken. Precordial lead taken with exploring electrode over cardiac impulse, and indifferent electrode on left leg.

B, Electrocardiogram taken July 22, 1938, twenty-one days after development of coronary occlusion. Precordial lead is IV F.

He continued his walk, and, immediately upon arrival at his destination (about 9:15 A.M.), developed a *second attack* which was identical with the first. He lay down upon a couch, and within twenty minutes the attack subsided without medication.

Before 5 P.M. *the patient experienced about twenty distinct recurrences.* The attacks were identical as regards the nature and location of the discomfort in the neck, chest, and arm. Dyspnea, sweating, and mild, generalized weakness were evident with each attack. Between attacks, the patient felt perfectly well. During

the lunch hour he felt so well that he played ball with several friends. No discomfort was evident during his exercise.

No attacks occurred after 5 P.M., and the patient had an entirely uneventful evening and night. He felt well the next three days.

On the morning of June 19, some dyspnea on exertion was noted. Because of this symptom he decided to enter the hospital, but, inasmuch as his dyspnea was very slight, he deferred his entrance until June 21. On admission the patient's blood pressure was found to be 142/106, his pulse rate 102. The following evening, while in bed, the patient had another attack similar to those of June 15, except that this attack lasted for almost an hour. After the pain subsided, the patient felt well.

On the morning of June 23, the patient had another attack that was the same as his previous attacks except that it persisted (despite morphine) throughout the day and night. The next day (June 24), about 11:30 A.M., there was a sudden exacerbation of the pain in the neck and chest, which radiated to the left arm and also involved both wrists. Dyspnea and sweating were increased; the pulse rate was 78; and the blood pressure was 208/122. An electrocardiogram, which was taken after twenty-four hours of continuous, but moderate, pain, and thirty minutes after the onset of severe pain, showed elevation of $S\text{-}T_1$ and S-T in Lead IV F, and depression of $S\text{-}T_2$ and $S\text{-}T_3$; T_1 and T_2 were upright, T_3 was diphasic, and T was upright in Lead IV F.

After five hours the symptoms were suddenly ameliorated, and gradually they disappeared except for an occasional recurring ache in both arms. The blood pressure dropped to 105/72 within two days, and a pericardial friction rub became audible over, and slightly to the left of, the lower end of the sternum.

An electrocardiogram which was taken June 27 showed changes of the Q_1 T_1 type, indicating myocardial infarction.

CASE 10.—F. F., a 45-year-old white office worker, had a four-day attack of interscapular pain, associated with dyspnea and marked sweating, during June, 1938. He was examined in the Outpatient Department at that time and was found to have "high blood pressure." An electrocardiogram showed evidence of "myocardial damage, possibly caused by previous infarction of the posterior wall." When this pain subsided the patient was seemingly restored to good health, but, in the middle of February, 1939, he developed attacks of "squeezing" pain which originated about 2 cm. medial to the left nipple, in an area about the size of a silver dollar. This pain quickly radiated across the anterior chest wall as far as the right parasternal line. There were a concomitant sense of pressure over the anterior portion of the chest and a "toothache-like" pain in the right upper extremity. The attacks were unrelated to exertion or meals and lasted ten or fifteen minutes. Aspirin, nitrites, and sodium bicarbonate gave no relief. The attacks occurred about once every two days.

In the two weeks preceding hospitalization, the attacks, although unchanged as regards their symptomatology, were becoming more frequent; *the patient experienced from ten to fourteen attacks of varying severity and duration in the seven days before admission.*

About 4 A.M. on the day of admission (April 4, 1939), the patient was awakened by a particularly severe attack of pain. This lasted about two hours and was the most prolonged he had had. Electrocardiograms which were taken during the first week of his hospital stay showed changes suggesting myocardial infarction, but no localizing pattern.

CASE 11.—J. C. S., a 49-year-old white clerk, gave the following history: In 1919, while in France, after a day of great activity, he developed a moderately severe, "gripping, aching" pain, located behind the entire length of the sternum.

The pain did not radiate, nor were there any associated symptoms, but it was severe enough to keep the patient awake all night.

The patient was free from any recurrence until 1931. At that time, while lying in bed, he had an attack similar to the one which he had experienced in France. The pain was of moderate severity and lasted between twenty and thirty minutes. The pain did not radiate, and there were no associated symptoms. The next day the patient felt perfectly well. Between 1931 and May 26, 1939, the patient experienced about ten attacks of retrosternal pain which lasted from five to ten minutes. Since these were so fleeting and were unassociated with any other symptoms, he never consulted a physician regarding them.

On May 26, 1939, while playing the second nine holes of a golf match, the patient suddenly developed "gripping," "aching" pain behind the entire length of the sternum. The pain was constant and only moderately severe. There was no dyspnea, nausea, or weakness. The patient continued to play, and, after thirty minutes, the pain disappeared. That night he felt perfectly well.

On May 29, 1939, about 9 A.M., while at his desk, the patient developed the same pain that he had experienced three days previously, except that it was more severe, and, in addition, he broke out into a "cold" sweat. He was generally weak and noted, particularly, definite weakness in both forearms. He felt slightly faint, but continued to work. The attack lasted about three hours, subsiding suddenly. At 12:30 he had a light lunch and was perfectly well for the rest of the day.

Between May 29 and June 14, the patient had two minor attacks, each of which lasted about five minutes. They were characterized by retrosternal pain, with no associated symptoms. One occurred while he was at his desk, and the other while he was lying on a couch, reading.

On June 14 he went out to play golf after a hard day's work. He played nine holes without any untoward symptoms. After finishing, the patient noticed that his forearms felt somewhat weak; this symptom had occurred at the time of his preceding attack, but never after playing golf. This weakness lasted fifteen or twenty minutes, but the patient was otherwise comfortable. After dinner that evening he felt nervous, and stated that he could not relax, although he had no specific complaints. He took a short walk and retired about 9 P.M. Immediately after lying down, the patient experienced a very severe, retrosternal, "aching" pain. This was felt behind the entire sternum for the first sixty minutes, but, after that, the point of greatest intensity was behind the upper two-thirds of the sternum. There was no radiation into the shoulders or arms, and no dyspnea. The patient broke out into a profuse, "cold" sweat. The pain was severe enough to keep the patient awake all night, despite the administration of a hypodermic. About 5 A.M., June 15, 1939, the pain in the chest began to subside, but at that time the patient noticed that he had slight aching in both forearms. The pain in the chest and forearms persisted until early in the afternoon of June 15, then disappeared. During the rest of that day, and on June 16 and 17, the patient had no definite complaints except that he felt generally "knocked out." An electrocardiogram which was taken on the afternoon of June 15 showed evidence of "damage to the heart." The patient was admitted to the hospital June 17, 1939. An electrocardiogram which was taken June 17, 1939, showed Q_1 T_1 changes typical of myocardial infarction.

CASE 12.—R. C., a 44-year-old white desk worker, was first seen Sept. 20, 1938, because of an attack of severe pain in the chest three days previously. His cardiac history dated back to 1931 (age, 37 years), when he developed typical angina of effort. His angina consisted of a "burning" sensation in the suprasternal notch which appeared on exertion and disappeared after one minute's rest.

In 1936, the patient developed a persistent ache in the left shoulder and a less severe ache in the left knee. No local cause for this discomfort could be found,

and various physiotherapeutic measures were ineffective. The left shoulder "ache" increased when his angina of effort appeared.

In September, 1937, he found that exertion which had formerly produced only suprasternal discomfort now caused extension of the "burning" sensation to the anterior part of the chest, between the parasternal lines in the third to fifth intercostal spaces. However, rest still brought prompt relief.

In mid-August, 1938, the patient was awakened from sleep by an attack of thoracic and suprasternal pain which was identical in character and location with that produced by effort, but now the pain radiated down the outer aspect of the left arm as far as the elbow. He sat up in a chair, and the attack subsided in thirty minutes. During the ensuing month the patient had frequent, painful attacks. About one-quarter of these were unrelated to effort. The character, location, and radiation of the pain were identical in all attacks. Those that were precipitated by exertion disappeared promptly with rest, but the remainder persisted for fifteen to thirty minutes. None lasted more than sixty minutes.

On Sept. 17, 1938, while playing cards, the patient had a very severe attack which was similar to the preceding ones, except that there was some radiation up both sides of the neck, as well as down the left arm. He became weak and was covered with perspiration. The attack lasted about six hours, after which he fell asleep (without medication). The next morning he felt perfectly well.

When he was seen on Sept. 20, 1938, he had no complaints. Physical examination revealed a stocky, muscular, white man who did not appear ill. His pulse rate was 68, and the pulse was regular. His blood pressure (taken with the patient in the recumbent position after fifteen minutes' rest) was 105/70 in the right arm, and 84/50 in the left. The heart was not enlarged; the sounds were normal and no murmurs were heard. There were inconstant, coarse, inspiratory râles at the bases of the lungs, but no other evidence of congestion was noted.

No cardiac abnormalities were observed fluoroscopically, and the electrocardiogram (Fig. 3*A*) was considered to be normal.

Six days later, crepitant, inspiratory râles were audible at both bases. No other abnormalities were found. The electrocardiogram (Fig. 3*B*) showed slight inversion of T_1.

The patient was seen again on Oct. 11, 1938. His angina of effort was unchanged, but there had been no further spontaneous attacks. Fine inspiratory râles were still present at the bases of both lungs; his electrocardiogram (Fig. 3*C*) was the same as before.

During the following two and one-half months the patient had no attacks of spontaneous pain. On Jan. 11, 1939, while working quietly at his desk, he experienced a severe attack of pain in the chest, neck, left shoulder, and left arm, which was identical with his previous attacks. There was no dyspnea, sweating, or faintness. The patient sat still, and in about two hours the pain suddenly ceased. Two days later, with the patient in the sitting position, the blood pressure was 112/68 in the right arm, and the pulse rate was 66 per minute. Physical examination revealed no abnormalities. An electrocardiogram (Fig. 3*D*) was taken, and repeated three days later (Fig. 3*E*), and again five weeks later (Fig. 3*F*). The electrocardiogram which was made Jan. 13, 1939, showed that T_3 was slightly inverted, and that the initial ventricular deflection in Lead III was less positive. T_3 became upright three days later. There were no other abnormalities.

In mid-April, 1939, the patient began to experience attacks of pain in the chest, shoulder, and arm on very little exertion. After a month of greatly restricted activity, he entered the hospital for more careful observation. The pulse rate was 57 and the beating was regular; the blood pressure was 118/72. The electrocardiogram (Fig. 4*A*) was the same as before.

The blood Wassermann and Kahn reactions were negative. There was a leucocytosis of 14,600, 38 per cent of which were lymphocytes. A roentgenogram of the chest showed moderate prominence of the trunk shadows at the bases of both lungs and a normal cardiac silhouette.

On the night of May 21, while lying quietly in bed, the patient had a mild attack of pain in the chest that subsided in three minutes without medication. He fell asleep, but was awakened about three hours later by a severe attack of pain of a "burning" character in the anterior part of the chest, lower part of the neck, left shoulder, and arm. He lay still for five minutes, but, when the pain failed to

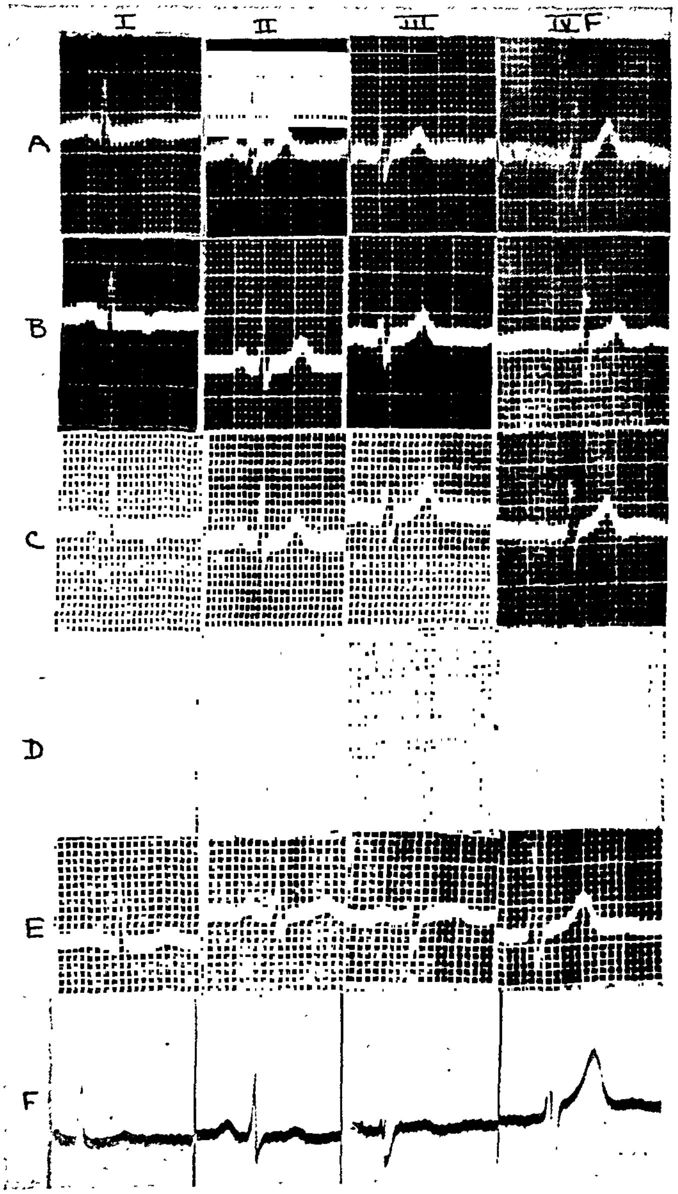

Fig. 3.—Case 12. *A*, Sept. 20, 1938. Angina of effort seven years. Frequent prodromal (?) attacks for one month. Severe attack three days previously. T_1 low, but no definite abnormalities.

B, Sept. 26, 1938. No complaints. T_1 has changed from a slightly upright to a slightly inverted wave. *No other abnormalities.*

C, Oct. 11, 1938. No complaints. Electrocardiogram unchanged.

D, Jan. 13, 1939. Pain at rest for two hours, thirty-six hours previously. Initial ventricular deflection in Lead III smaller. T_2 and T_3 inverted; T_1 upright. No S-T interval changes.

E, Jan. 16, 1939. T_2 and T_3 have become upright. No other change.

F, Feb. 8, 1939. No complaints. Electrocardiogram unchanged.

subside, took 1/100 grain of nitroglycerin. About five minutes later the pain suddenly ceased. Although the attack did not last more than ten minutes, it was quite intense. These two short attacks were the first spontaneous ones which he had had since Jan. 11, 1939.

The next morning the pulse rate was 72, and the beating was regular; the blood pressure was 112/70. Examination of the heart and lungs showed no abnormalities. An electrocardiogram (Fig. 4C) showed slight S-T deviations in Leads II and IV F.

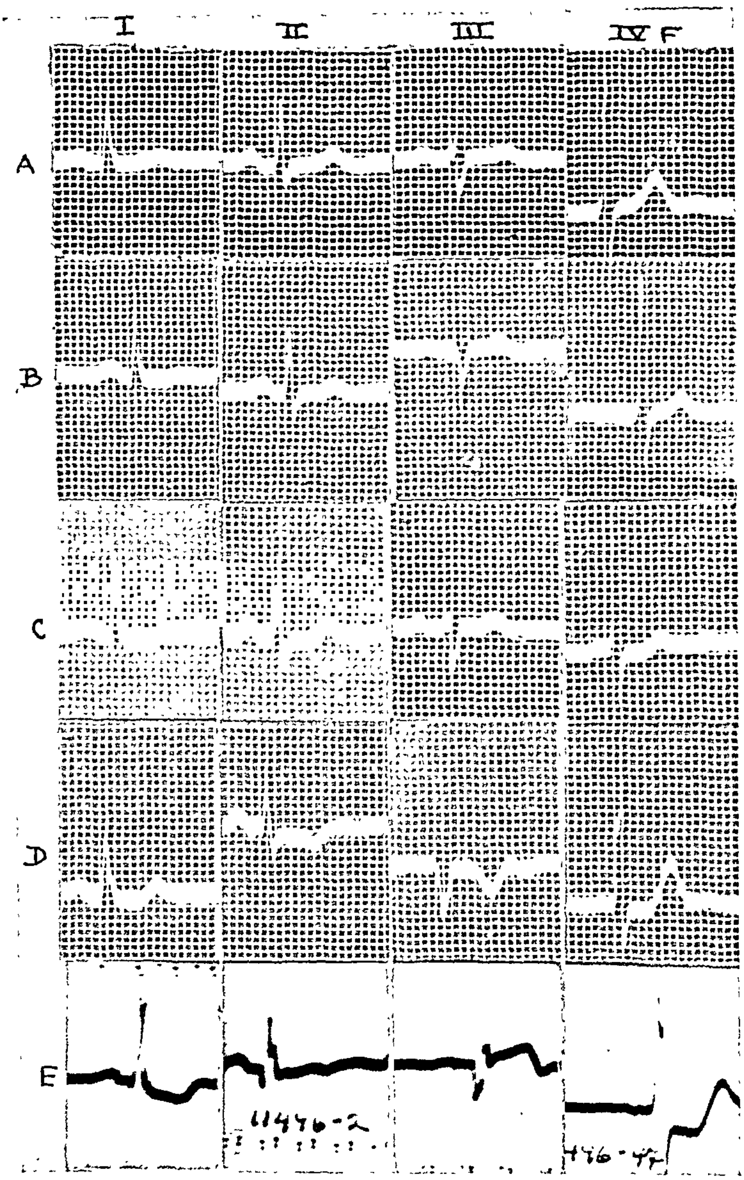

Fig. 4.—Case 12. *A*, May 15, 1939. Exercise tolerance greatly decreased because of increasingly severe angina of effort. Electrocardiogram unchanged.

B, May 20, 1939. No complaints.

C, May 22, 1939. Two attacks of pain in chest during preceding night. These were considered prodromal attacks. Limb leads show no T-wave changes. S-T in Lead IV F is slightly depressed, and T in Lead IV F is smaller.

D, June 14, 1939. Had at least ten severe attacks at rest, lasting from thirty minutes to four hours. Note downward displacement of S-T in Leads II and IV F. T_2 slightly, and T_3 deeply, inverted.

E, June 16, 1939. Severe attack of pain in chest preceding night, persisting to the time the electrocardiogram was taken. Note changes of the Q_3 T_3 type typical of myocardial infarction.

After leaving the hospital on May 30, the patient complained of constantly recurring attacks without obvious exciting causes. At least four of these occurred while he was in bed, and relief could be obtained only by sitting up. Under these conditions the pain disappeared in from thirty to forty minutes; nitroglycerin was ineffective. There was neither dyspnea nor cough.

Five days later (June 14), the spontaneous attacks of pain were lasting from three to four hours, instead of thirty minutes. An electrocardiogram (Fig. 4*D*) showed inversion of T_2 and T_3, and slight downward displacement of the S-T segments in Leads II and IV F. QRS_3 was questionably monophasic and downward. Physical examination revealed no abnormality. The patient refused hospitalization.

On the night of June 15 he had an extremely severe attack of pain in the anterior part of the chest, left shoulder, arm, and both sides of the neck. Sweating was profuse and prostration marked. Next day the pain was still present, and the patient was in shock. An electrocardiogram (Fig. 4*E*) showed Q_3 T_3 changes typical of myocardial infarction.

The patient died the following day without responding to efforts directed toward combating the profound shock.

At autopsy the relevant abnormalities were found to be confined to the heart and lungs. There were scattered patches of hypostatic pneumonia in both lungs.

Fig. 5.—Case 12. Right coronary artery. Note markedly compressed lumen. The intramural cavity contained a mass made up of inspissated blood, hyaline material, and cholesterin crystals. *L*, Lumen; *C*, intramural cavity.

The pericardial sac contained about 50 c.c. yellow, purulent fluid. Irregular patches of fibrin were scattered across the base of the heart and great vessels. The heart weighed 401 Gm.

The myocardium was dark brown and rather flabby. No areas of softening or fibrosis were found in the wall of the left ventricle. A number of thin, gray streaks ran through the wall in the posterolateral portion of the left ventricle, but these could not be definitely identified as areas of scarring. No ante-mortem thrombus was found in any of the chambers.

The valves were normal. The ascending aorta showed a mosaic of small, flat, atheromatous plaques. The coronary ostia, although not involved by the sclerotic process in the aorta, were definitely reduced in size, measuring from 1 to 2 mm. in diameter. The anterior descending branch of the left coronary artery was reduced to a firm, fibrous cord immediately below its point of origin. Transverse sections of this vessel revealed patchy calcification of the wall and reduction of the lumen to pin-point size. Similar sections of the left circumflex artery showed that the wall was markedly thickened and the lumen reduced in size throughout its course. There was, however, no complete obstruction of this vessel. Immediately beyond the point of origin of the right coronary artery, the lumen was markedly reduced in size. This was caused by impingement upon the lumen of mixed atheromatous and hemorrhagic

Fig. 6.—Case 12. Right coronary artery. Post-mortem thrombus filling lumen. The atheromatous "abscess" contained considerable fresh blood about its periphery. Note other areas of dissection in the wall of the vessel. *A*, Atheromatous abscess; *D*, dissecting aneurysm containing fresh blood.

lesions within the arterial wall. This disorganization of the wall extended, in varying degree, for about 5 cm., at which point a fresh thrombus completely obstructed the vessel.

Microscopic examination showed that the right coronary artery was obstructed, about 5 cm. from its ostium, by a freshly formed, laminated clot. From the ostium to the thrombus the artery showed extensive change, and immediately distal to the point of origin the lumen was markedly compressed. This was caused by a large, intramural mass made up of inspissated blood, cholesterin crystals (clefts), and necrotic debris (Fig. 5). More distally, areas of fresh hemorrhage into this mass could be seen, and there were a number of recent and completely separated "dissecting aneurysms" in the wall of the artery (Fig. 6). Below this point, the dissection was so extensive that the intima was completely separated from the supporting media and adventitia (Fig. 7). Lying between this area of complete dissection and the thrombus itself, there were two points of communication between the lumen and the intramural cavity (Figs. 8 and 9).

The wall of the artery was the seat of extensive hemosiderin deposits, much of which was contained in phagocytes. There were irregular patches of calcification lining the cavity in the arterial wall. Both the adventitia and media were heavily infiltrated by mononuclear cells, most of which were small lymphocytes and plasma cells. Many of the vasa vasorum showed "collars" of lymphocytes.

The circumflex branch of the left coronary artery showed mural cavitation of a moderate degree, causing some encroachment upon the lumen. There was, however,

Fig. 7.—Case 12. Right coronary artery. The intima is "dissected" free of the supporting media and adventitia. *I*, Intima; *L*, lumen.

no communication between the atheromatous "abscess" and the lumen. No obstruction of this artery could be found.

The lumen of the anterior descending branch of the left coronary artery was markedly narrowed throughout its course. There was an extreme degree of proliferation of the subintimal tissue. At one point the greatly thickened wall showed two eccentric spaces, either of which might have been the original lumen or the result of canalization of an old thrombus.

Sections from (1) the lower lateral aspect of the left ventricle and (2) the lowermost portion of the interventricular septum and contiguous diaphragmatic portion of the left ventricle and anterior aspect of the right ventricle showed no fibrosis. In both of these areas, however, the myocardial fibers had lost their striations, and the sarcoplasm had a "boiled" appearance. There was heavy polymorphonuclear infiltration in and about these areas. The changes extended through the entire thickness of the ventricular wall. The pericardial surface was covered with a thick, fibrinous network which contained closely packed polymorphonuclear leucocytes. Several sections showed a deposit of fibrin on the endocardium.

Summary.—A 44-year-old white man, who gave a history of typical angina of effort for seven years, began to experience, nine months before death, attacks of cardiac pain which were not associated with any obvious exciting factors. These became progressively more frequent and more severe and radiated more widely. Between attacks the patient felt well except for angina of effort; physical examination on two occasions showed nothing except pulmonary congestion. Until a few

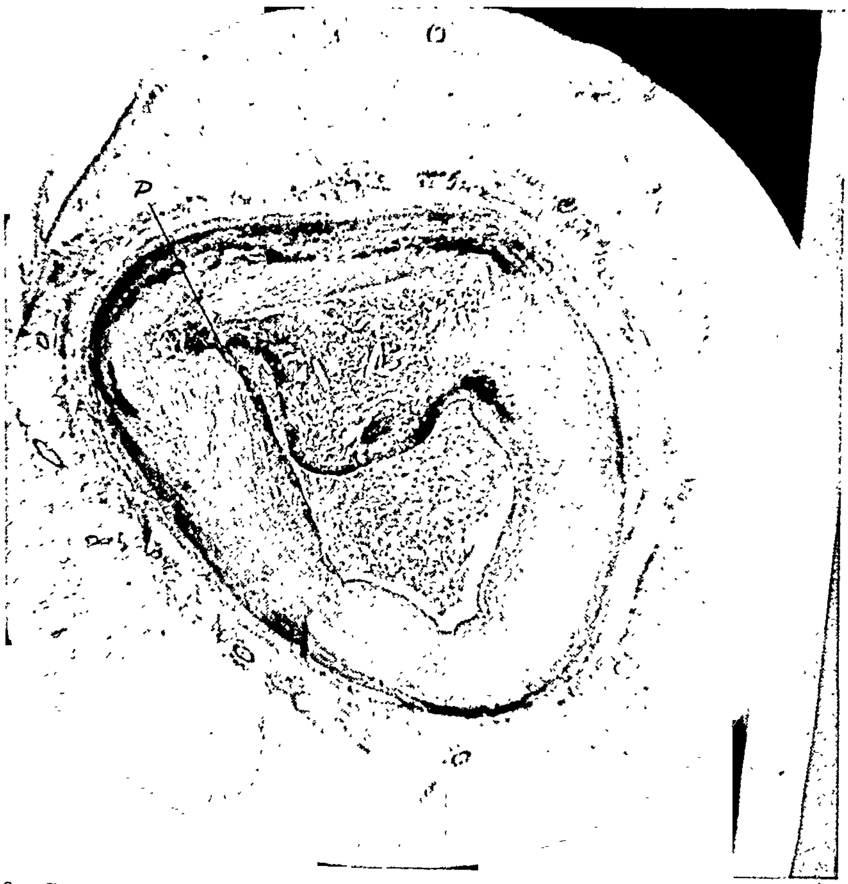

Fig. 8.—Case 12. Right coronary artery. Point of communication between atheromatous "abscess" and lumen. *P* indicates communication.

days before death, the electrocardiograms showed either no abnormalities or only transient changes. The heart was the seat of widespread coronary artery disease, without demonstrable myocardial damage except for acute lesions caused by the terminal occlusion of the posterior coronary artery.

COMMENT

The "prodromal" attacks of pain varied from case to case as regards duration, character, and the length of the period by which they preceded the obvious manifestations of coronary occlusion. In general, the attack appeared suddenly, without obvious precipitating causes, when the patient was apparently in good health. The pain usually developed while at rest. In several cases (4, 5, 8, 9, and 11), attacks were associated with exertion, but in these instances the pain either was not relieved by cessation of the exercise or began after the exercise was stopped. Some patients (Cases 1, 2, 3, 4, 7, 8, 9, 11, and 12) were able to do fairly strenuous work without discomfort on the same day on which they had spontaneous attacks of pain. One patient (Case 12) had attacks of angina of effort which were relieved promptly by

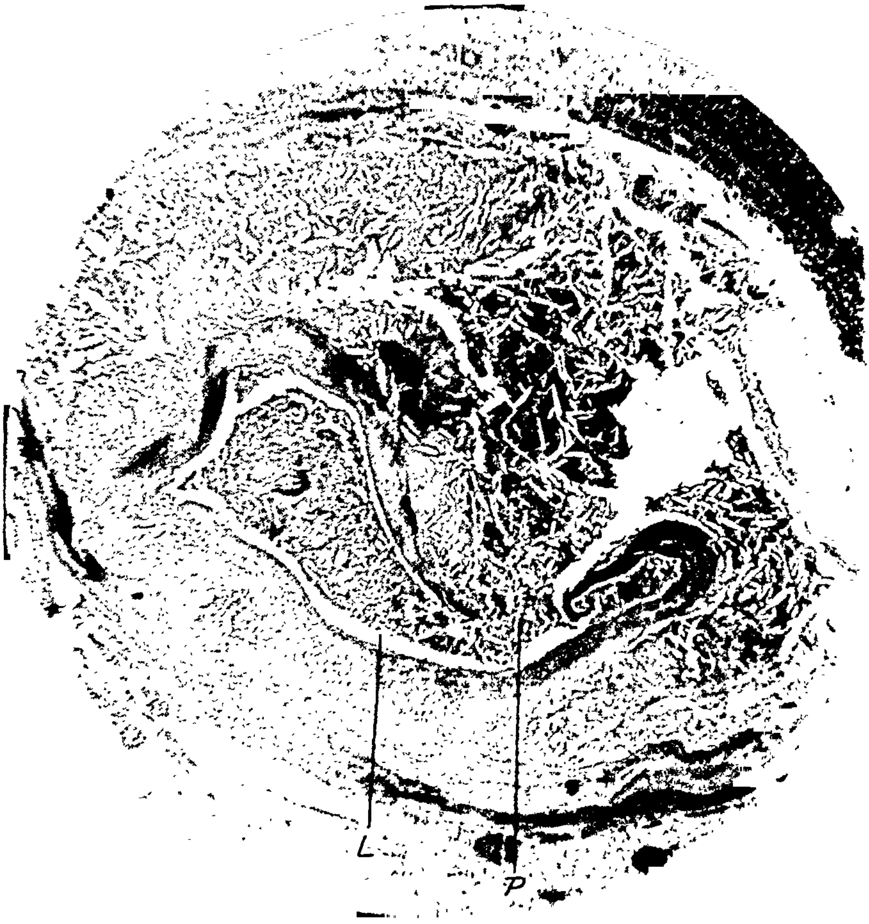

Fig. 9.—Case 12. Right coronary artery. Intimal rupture, with communication between lumen and "atheromatous" abscess. The ante-mortem thrombus lay immediately distal to this point. *L*, Lumen; *P* indicates communication.

rest, but he also had pain which was not associated with exercise, emotional excitement, or eating, which he, himself, differentiated from his angina of effort.

The pain varied in duration from fifteen minutes to hours, and from a mild ache to extreme severity. It was variously described as "burning," "gnawing," "constricting," "toothache-like," "gripping," "aching," "swelling," "burning and crushing." The character of the pain tended to remain constant during the entire prodromal period in each case, but the severity, duration, and area involved increased with succeeding attacks. Most commonly, the pain was referred to the anterior chest wall between the midclavicular lines, and in all cases it was ultimately located in this area. There were three cases in which the pain did not involve the chest primarily. One patient (Case 1) had "severe aching" and weakness of the left arm, and a second (Case 2) had intermittent pain in both shoulders for a week before the coronary occlusion. The third (Case 5) had pain in the left elbow for six days preceding the onset of pain in the chest. One patient (Case 12) had had pain in the left shoulder for three years. In other cases (1, 5, 6, 8, 9, and 11), it was noted that pain and extreme weakness in one or both upper extremities were associated with the premonitory manifestations. There was no local disease, and the subsequent course of events indicated that the peripheral pain and weakness were related to the changes in the heart and coronary arteries.

Between prodromal attacks the patients felt well, except for transient weakness. In the cases in which a physician examined the patient between attacks (Cases 6, 7, 8, and 12), no signs of myocardial infarction were found. The electrocardiograms did not show changes typical of coronary occlusion following a prodromal attack in the three cases in which tracings were made during this period (Cases 7, 8, and 12).

DISCUSSION

The mechanism responsible for prodromal pain is not clear. Feil[1] thought that ". . . progressive reduction in the lumen—either before the formation of the thrombus or with a gradually growing thrombus—appears to be the most acceptable explanation." Sampson and Eliaser[2] suggested that the attacks were caused by temporary coronary insufficiency caused by "varying hemodynamic factors" in a diseased coronary artery. Parkinson and Bedford[3] stated that "prodromal pains herald the beginning of thrombosis."

Dr. J. B. Herrick,[4] in the course of a discussion at the American Heart Association meeting, in 1934, called attention to the possible relationship between prodromal pain and rupture of an atheromatous "abscess," with subsequent formation of a dissecting aneurysm in the wall of the involved coronary artery.

Examination of the many sections of coronary arteries in our collection reveals that intramural hemorrhage, with the formation of "dissecting aneurysms," is a frequent occurrence. This usually takes place without intimal rupture. The hemorrhages may vary from small, subintimal lesions in arteries which show only minimal atheromatous change, to large "hematomas" filling atheromatous "abscesses" in the walls of severely damaged arteries. As can be seen from Figs. 5 and 6, intramural hemorrhages can cause marked encroachment upon the lumen of the involved vessel and serious disorganization of the wall. Such extravasations of blood could produce transient pain in one or both of the following ways.

First, a massive intramural hemorrhage, causing a more or less sudden diminution in the caliber of the artery, may produce relative myocardial ischemia. Since the obstruction is acute, but only partial, the pain will last only during the period of circulatory readjustment. In some cases, the intramural hemorrhage is sufficiently large to cause coronary occlusion and myocardial infarction.[7] The effect upon the myocardium may be reversible, however, if the obstruction is not complete. This reversal may be brought about by reabsorption of the fluid elements of the hemorrhage, so that the lumen regains a caliber large enough to allow the passage of an adequate amount of blood. The time needed for restoration of a satisfactory flow would depend upon the size of the hemorrhage and the original caliber of the lumen. The ability of uninvolved vessels to act as collaterals will also affect the duration of the ischemic period.

Second, stimulation of the coronary periarterial nerves may be a factor. Evidence has been obtained by animal experimentation that mechanical stimulation of the adventitia and the periarterial nerves causes pain, even when the coronary flow is unobstructed.[5, 6] Tension on the adventitia and its nerves, caused by the intramural hemorrhage, might be the exciting factor in man. In addition, arteries with extensive hemorrhagic lesions show widespread, small round-cell infiltration in the adventitia, about the vasa vasorum, and even about the nerve trunks. It is possible that inflammatory changes during the acute process may contribute to the pain.

It is recognized that other pathologic changes in the arteries and myocardium might be the source of "prodromal" pain. Conceivably, multiple, small infarcts caused by embolism or thrombosis of several small coronary arteries, gradual growth of a thrombus, or propagation of a clot, with progressive occlusion of larger branches of a vessel, could cause recurrent attacks of pain. Such changes are not compatible, however, with the absence of signs, symptoms, and electrocardiographic changes between painful seizures, particularly in those patients who had many attacks (Cases 6, 8, 9, 10, and 12) before the coronary occlusion. Furthermore, in the one patient who was

autopsied (Case 12), the only identifiable thrombus which was found was not more than three or four days old, although the patient's prodromal symptoms had existed for more than six months. The fact that there was no myocardial fibrosis also militates against the theory that successive, small infarctions are the cause of the prodromal attacks.

It is recognized that, in the presence of a reduced coronary vascular bed, any process that would increase the work of the heart or decrease the coronary blood flow might cause pain. For instance, tachycardia, unrecognized excitement, and changes in blood pressure could be such factors, but in our patients there was nothing to indicate that any of these things occurred.

The ultimate development of coronary occlusion as a result of active hemorrhage within the wall of the artery is to be expected. Complete obliteration of the lumen may be caused by expansion of the dissecting aneurysm, as pointed out by Wartman,[7] or the pressure within the aneurysm or hemorrhagic atheromatous "abscess" may rupture the intima and thus bring about obstruction (Leary[8, 9]). It is also possible that the intramural hemorrhage, by damaging the overlying endothelium, may promote thrombosis within the lumen.[10]

CONCLUSIONS

Attacks of cardiac pain other than angina of effort may precede the typical manifestations of coronary occlusion.

There are undoubtedly many factors which contribute to the production of prodromal pain and subsequent coronary occlusion. Of these it appears that intramural hemorrhage may be an important one.

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SIMULTANEOUS MECHANOGRAMS AND ELECTROGRAMS FROM THE INTACT HUMAN SUBJECT, WITH NOTES ON THE EFFECTS OF DISTENTION OF THE STOMACH ON THE CONVENTIONAL ELECTROCARDIOGRAM

Preliminary Report

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INTRODUCTION

Many attempts have been made to measure the electrical changes in the stomach of the unanesthetized intact human subject, but such studies have been limited to the use of indirect methods because of the technical difficulties involved. Some experiments have been made on animals with the viscera exposed,[1-6] and others have been made on human beings with thin abdominal walls by placing the electrodes on the surface of the body.[7-9] Neither of these methods yields results similar to those obtained in this study, and, as far as we know, there is no literature pertaining to the electrical changes in the esophagus and stomach of the unanesthetized human subject.

At first we attempted to show a correlation, or lack of correlation, between the electrical changes in the esophagus and stomach and other viscera when contractions of these organs occurred. As data accumulated, it became apparent that the electrical changes did not lend themselves to a simple analysis. Even though this is the case, we think the data of sufficient physiologic interest and clinical importance to warrant a short preliminary report before the completion of the investigation.

PROCEDURES

The mechanograms and electrograms were recorded simultaneously on a string galvanometer type of electrocardiograph.

The mechanograms were obtained by the ordinary balloon method, but with a special recorder, as shown in Fig. 1. This recorder consists of a modified aneroid barometer; a piece of brass tubing was soldered to the airtight chamber, so that pressure and volume changes in the balloon were transmitted to the inside of the aneroid chamber by means of rubber tubing, thus bringing about a deflection of the needle. This is a very sensitive instrument for recording volume or pressure changes. The instrument is placed in front of the camera slit, so that movements of the needle are optically recorded.

The electrical changes in the organ under observation were recorded on the electrocardiograph, as follows: Fine wires (silk-covered copper wire, gauge 36), connected with the electrocardiograph, were passed through the rubber tubing and over a glass bead (Fig. 1), to which the inner balloon was tied. The balloon was tied over the glass bead in such a manner as to leave the wires outside. The wires were

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then anchored to the outer balloon in any desired position, and with electrodes as long or as short as might be desired. In these experiments, about one inch of the wire made actual contact with the esophagus or stomach. The loop of wire was soldered in order to avoid the possibility of dislodgment or pricking the mucosa. By suitable adjustments, the movements of the aneroid needle can be recorded simultaneously with the electrical changes in the esophagus or stomach. The balloons with the electrodes are not difficult to swallow, and are certainly not as distressing as the passage of the ordinary stomach tube.

The subjects of these experiments were healthy men, and all but one, subject G, had a normal, conventional electrocardiogram.

Records were taken from the mouth, esophagus, and stomach.

Some of the experiments were done on the fasting stomach during hunger contractions, and others were done after a full meal. In some of these, both electrodes were in the organ, but, in others, one electrode was in the organ and the other was applied to the left wrist.

Still other experiments were made with the *standard leads* and a balloon in the stomach, before, during, and after distention of the stomach.

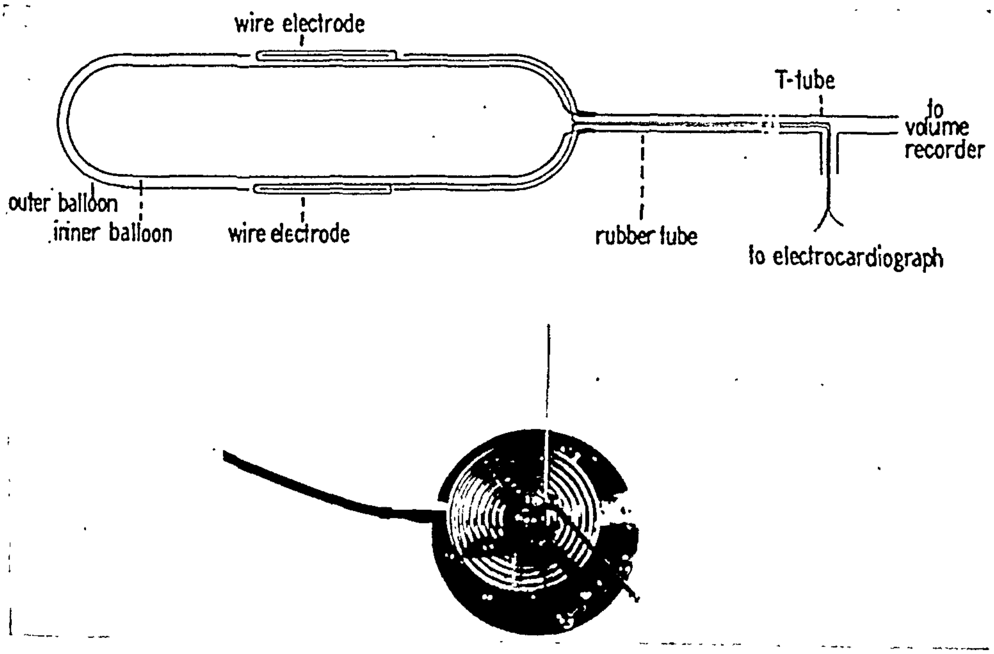

Fig. 1.—The upper illustration is a diagram showing how the electrodes are anchored to the ordinary stomach balloons so that they can be swallowed by the subject. The diagram is self-explanatory. The lower illustration is a photograph of a modified aneroid barometer, used to record the volume changes of the stomach.

RESULTS

Records From the Mouth.—These showed no electrical changes.

Records From the Esophagus.—The electrograms from the esophagus showed at least two components, namely, that produced by the action of the heart and that produced by respiratory action. In some experiments there was a close correlation between the respiratory action and electrical variations, as is shown in Fig. 2. In others there was very little correlation (Fig. 3). There was no definite correlation with peristaltic action. There were also some changes in the S-T segment, shown in

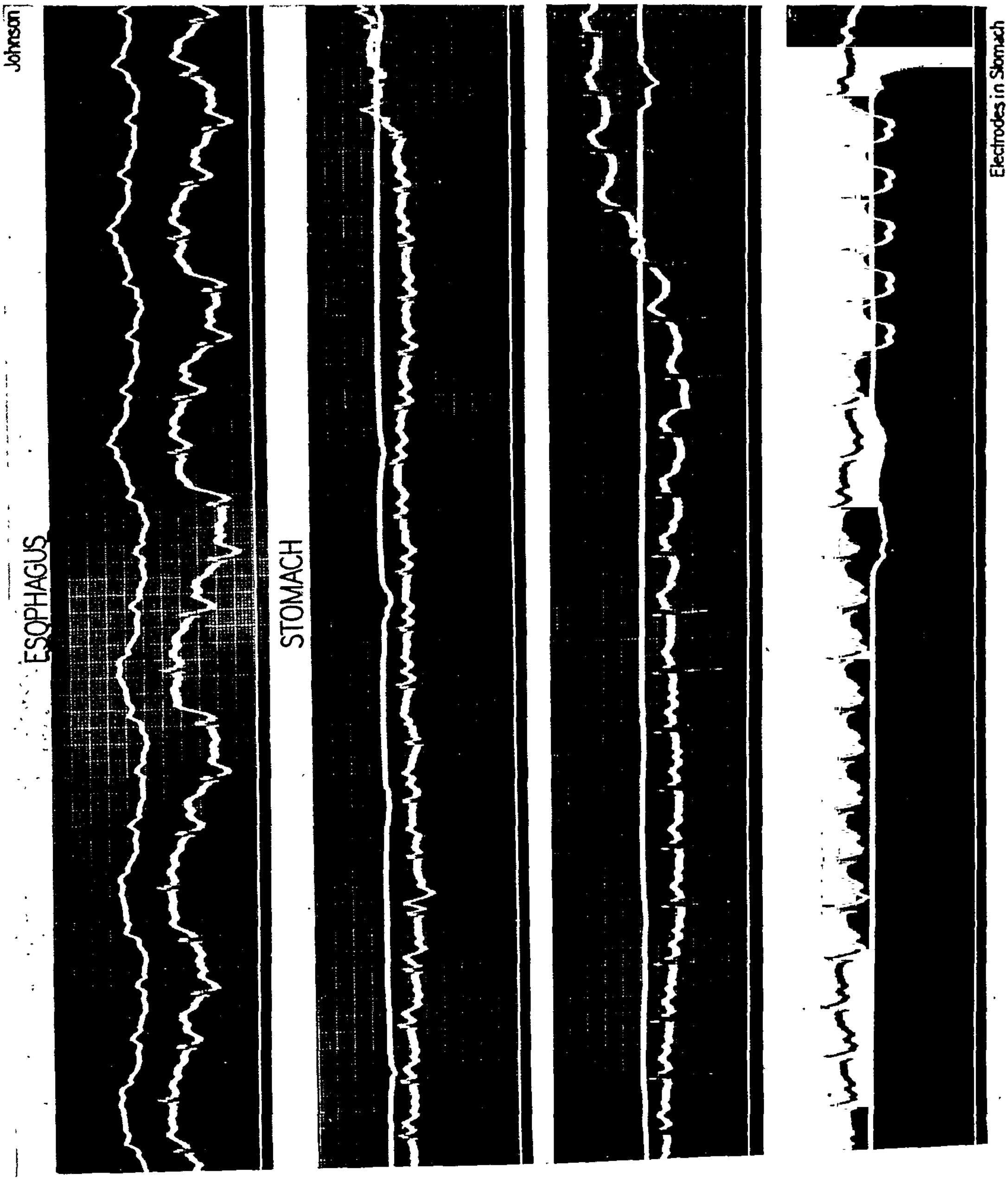

Fig. 2.—Typical simultaneous mechanograms and electrograms from both the esophagus and stomach. In this experiment both electrodes were from the organ under observation. The change in the base line of both the electrogram and mechanogram from the esophagus is probably respiratory in origin, but other records, in a similar manner and on another occasion, did not show these changes (Fig. 3). The lower records show electrograms and mechanograms from the fasting stomach, with increasing degrees of distention. Note particularly the spontaneous changes in the contour of the electrogram, especially the S-T segment. Compare this illustration with Fig. 4, which shows records taken with one electrode in the stomach and one on the left wrist.

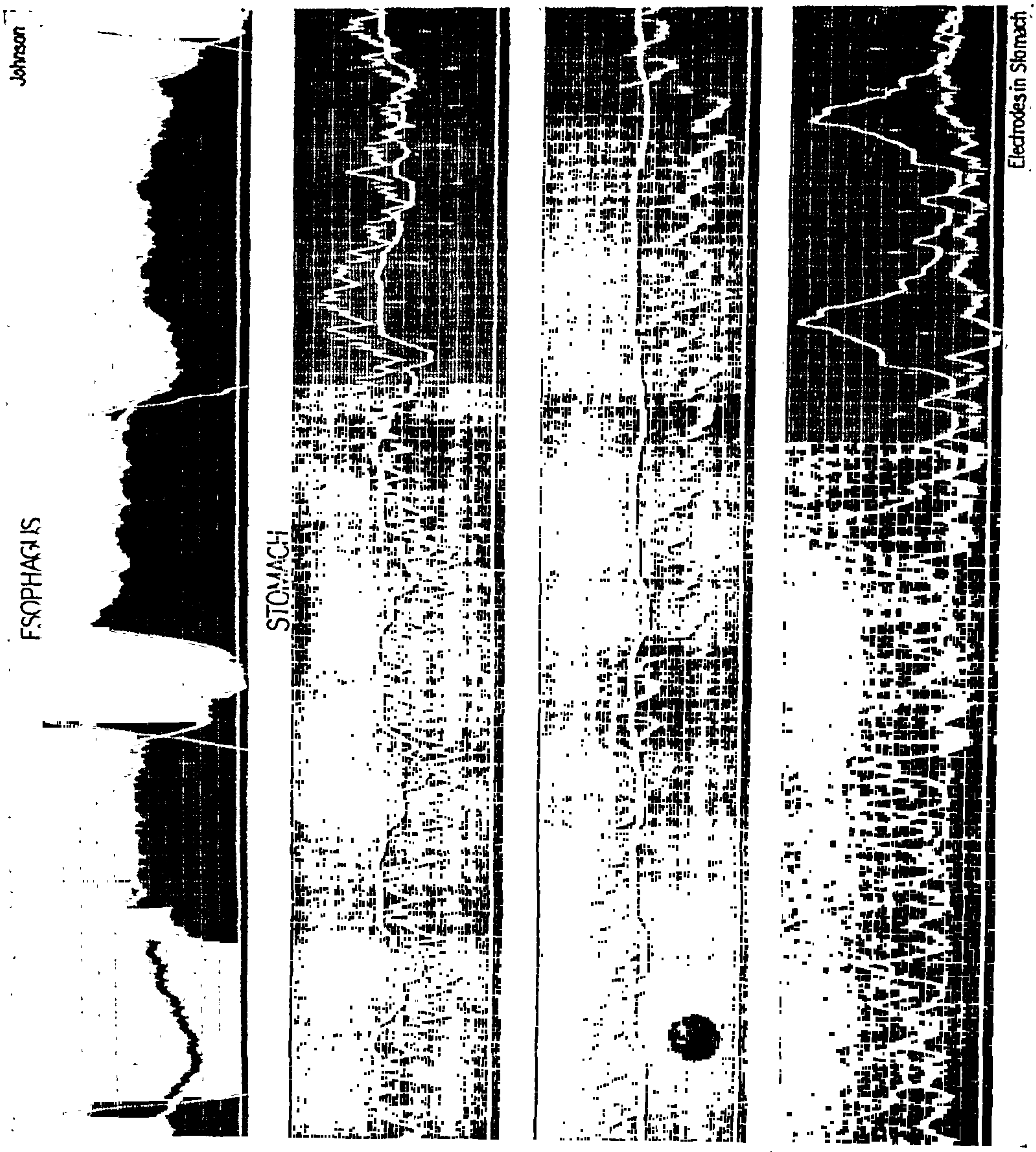

Fig. 3.—Records similar to those of Fig. 2, except that the experiment was done after taking a full meal. Note the marked spontaneous changes which occur in the *electrogram* from the stomach.

Fig. 2, which may have been merely the result of shifting of the isoelectric line associated with respiratory action. The records from the esophagus with both electrodes therein, or with one electrode in the esophagus and one on the left wrist, were similar (Fig. 4).

Records From the Stomach.—These electrograms were made up of at least two components, and probably three, or more: one was the electrocardiographic component; the second was the electrocardiographic component as modified by contractions of the stomach or distention of the stomach; and the third included the changes in the base line (isoelectric

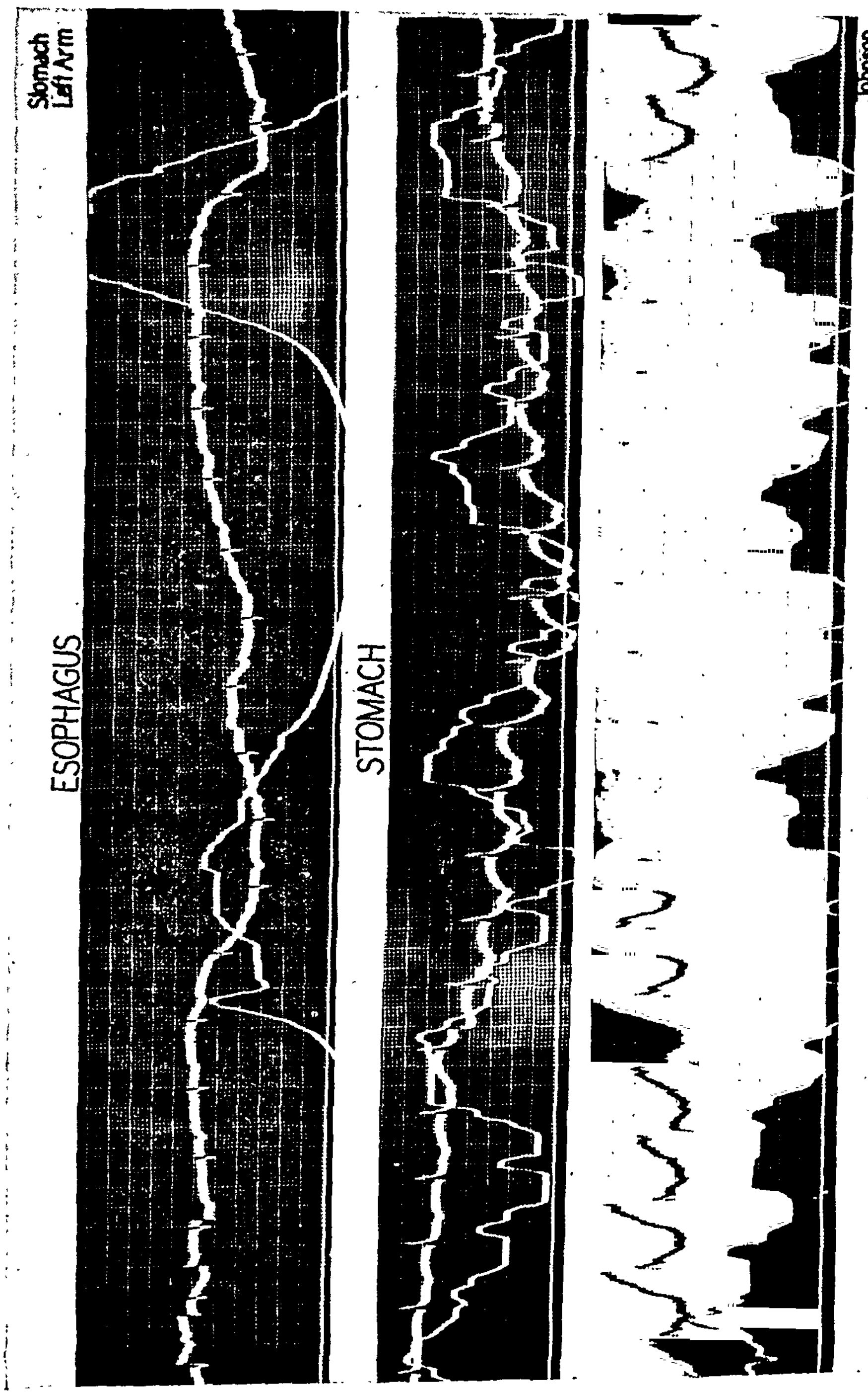

Fig. 4.—These records are similar to those in Figs. 2 and 3, except that only one electrode was in the viscus, and the other was on the left wrist. These records were also taken following a full meal. Note the marked changes in the electrogram which bear little or no relation to the changes in the mechanogram.

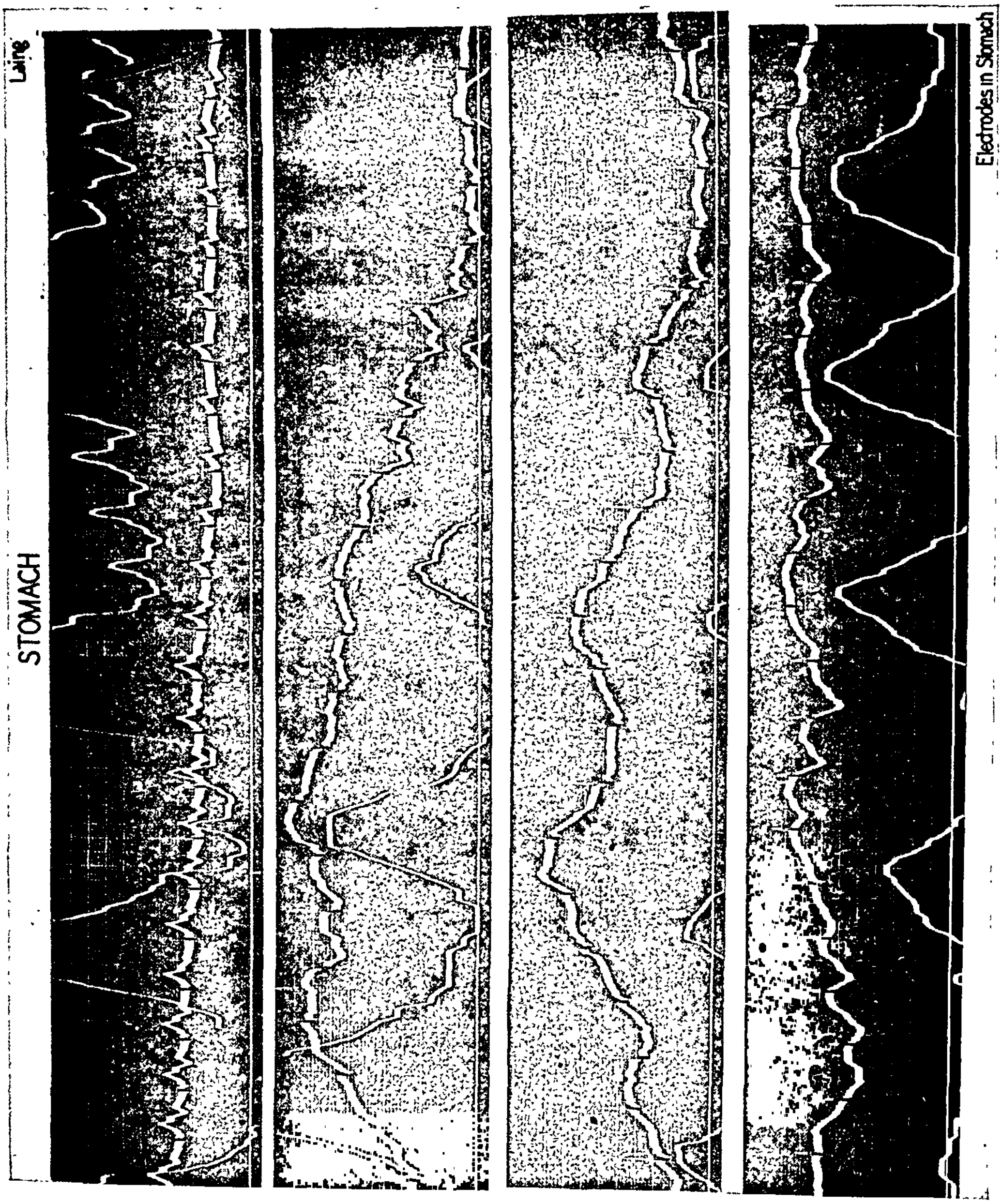

Fig. 5.—Records similar to those shown in Fig. 2, but on a different subject. Note that there was no correlation between the changes in the electrogram and the mechanogram. The hunger contractions recorded were of sufficient intensity to distress the patient.

line) as modified by respiration and gastric contractions. These changes are illustrated in Figs. 2, 3, 4, and 5.

The mechanograms reflected both cardiac and gastric activity. The cardiac component of this curve illustrates the sensitivity of the instrument, for the time which elapsed between the Q wave and the beginning of the mechanical registration of cardiac activity was only 0.08 second. The mechanical record of the cardiac contraction may represent transmission by adjacent structures, or it may be a reflection of the arterial pulse wave from the gastric or abdominal vessels.

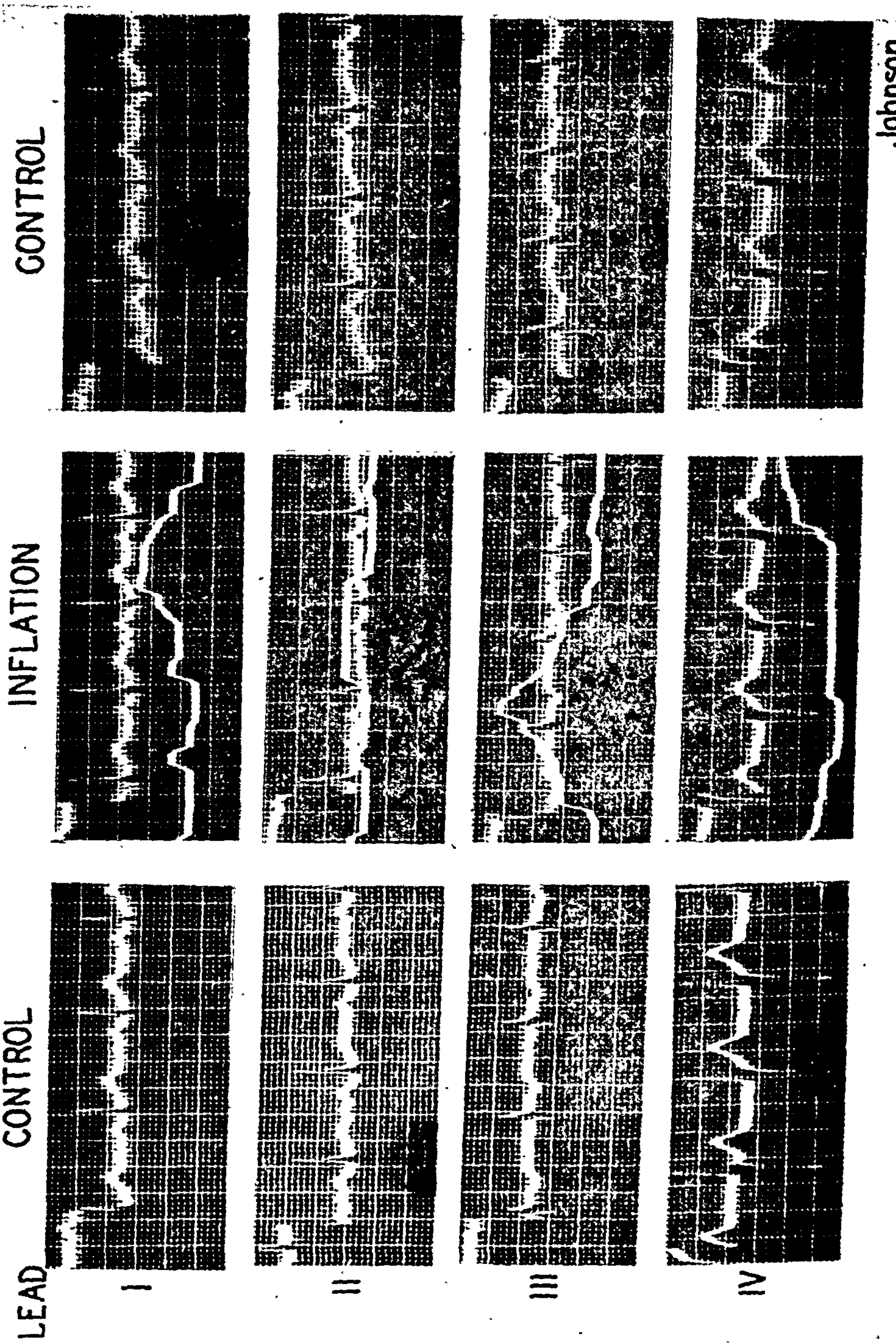

Fig. 6.—Electrograms *taken with the conventional leads* before inflation of a full stomach, during inflation to the point of distress, and after deflation. Note that, during inflation, Q_3 becomes deepened and R_3 becomes lower. Following deflation, these changes disappear.

Hunger contractions and electrical changes showed a correlation and a lack of correlation in the same record, as is illustrated in Fig. 5.

Marked changes can be produced by distending the stomach by inflating the balloon; these are illustrated in all of the records, but particularly in Figs. 2, 3, 4, and 5. These changes are chiefly in the form of the T wave and the S-T segment. Similar records were obtained when both electrodes were in the stomach and when one electrode was in the stomach and the other on the left wrist.

The Effect of Distention of the Stomach Upon the Conventional Electrocardiogram.—The association of abdominal distention and cardiac

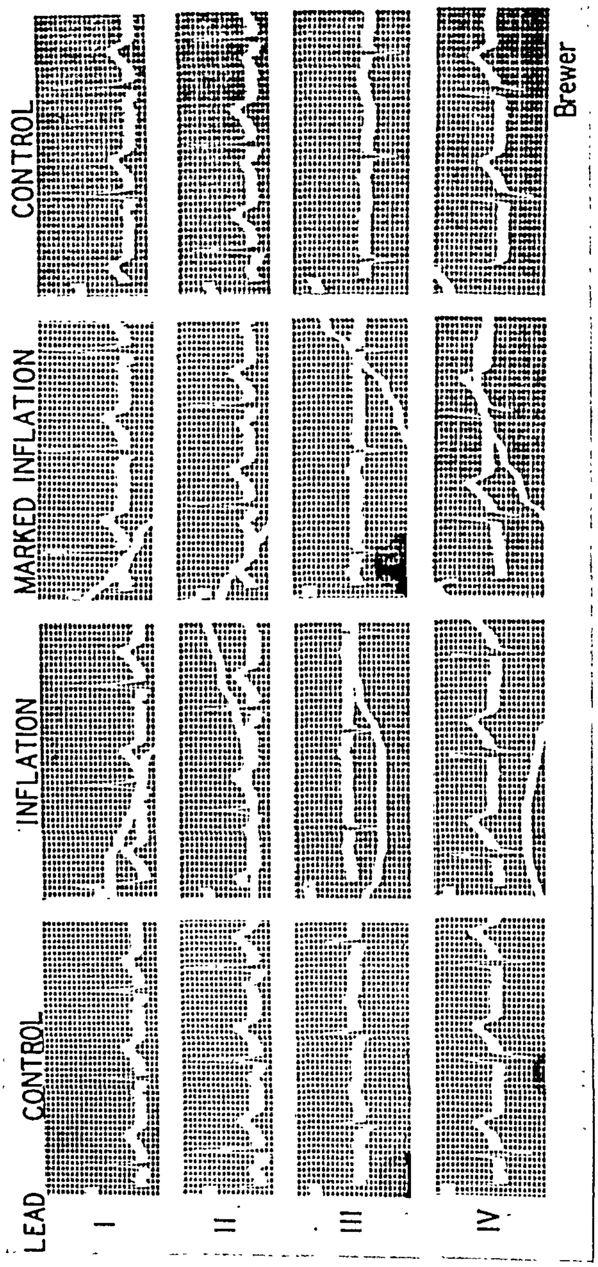

Fig. 7.—Records similar to those in Figs. 6 and 8, but from another subject. Note that, during inflation, R_1 becomes increased in amplitude, Q_3 becomes depressed, and R_3 becomes abolished. These changes persisted even after deflation of the stomach.

distress has long been noted clinically. Therefore, treatment should not be directed at the heart alone, but toward the relief of abdominal distention, which in itself may play an important role in the production of cardiac symptoms. Some experimental work has been done in an attempt to discover the mechanism by which distention produces cardiac distress. Burgess, Scott, and Ivy,[10] while studying the effects of prolonged distention of the stomach in the normal dog, noted electrocardiographic changes, but mainly after prolonged and marked distention. Owen[11] attempted to produce extrasystoles in normal dogs by distending the stomach. He was successful with only one dog out of ten.

Distention of the stomach to the point of distress, by inflation of the balloon, also produced changes in the conventional leads of the electrocardiogram, as is shown in Figures 6, 7, and 8. (Changes were more easily produced when these experiments were done shortly after a heavy

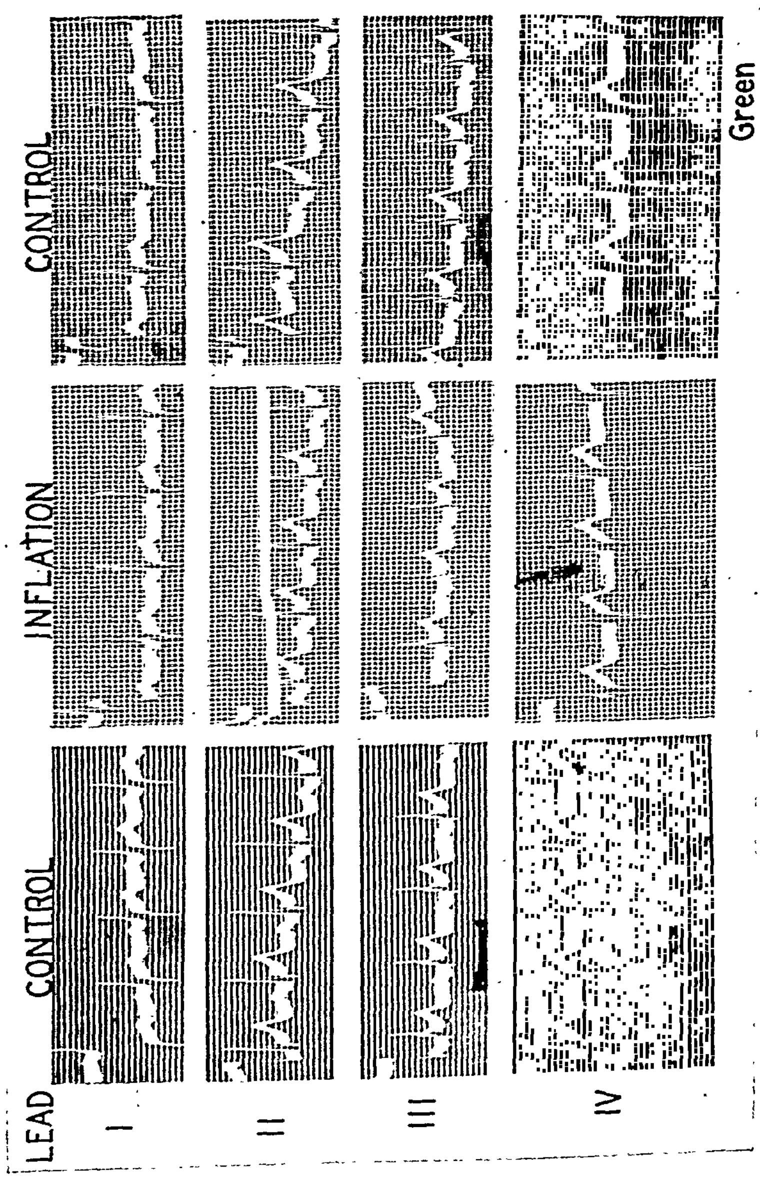

Fig. 8.—These are records of experiments similar to those shown in Figs. 6 and 7, but from another subject. Note that the slurring on the ascending limb of R_3 moves down to the isoelectric line during inflation.

meal.) The amount of air necessary to produce sufficient distention varied from subject to subject.

One notes that in two subjects (Figs. 6 and 7), in Lead III, the Q wave grew deeper, and the R wave became depressed to the isoelectric line. Relieving the distention caused these abnormalities to disappear. This experiment was repeated three times on the same subject, with similar results. In another subject similar results were obtained, except that the changes persisted after release of the distention. In still another subject (Fig. 8), the slurred portion of the ascending limb of R_3 moved toward the isoelectric line.

The Effect of Distention of the Stomach on the Conventional Electrocardiogram in Two Cases of Myocardial Disease.—The records from patients with myocardial damage are shown because (1) they illustrate more marked changes in the electrocardiogram; (2) during, and for a long time after the experiments, the patients had symptoms of cardiac distress; and (3) the interval between the P wave and the registration of cardiac contraction does not coincide with the generally accepted value.

The electrocardiograms are illustrated in Figs. 9 and 10, and show changes mainly in voltage, the T wave, and the S-T segment.

During the inflation of the stomach the patients complain of "gas pressure up around the heart," and said "it shut off the wind." They also complained of more cardiac distress than usual, and this lasted for several days after the distention was produced.

The interval between the P wave and the mechanical registration of cardiac contraction, as shown in the records, is about one-half as long as that which is generally accepted, namely, from 0.04 to 0.08 second.

We have not as yet fully analyzed these experimental results, but it would seem that this offers a good method for making a study of this fundamental problem.

DISCUSSION

The electrical changes which occur in the esophagus and stomach are of unusual interest, not only because of their bearing upon gastrointestinal physiology, but also because the changes induced by gastric distention indicate that there are gastrocardiac reflexes which are important in clinical medicine. This is in keeping with some of the results of Scott and Ivy,[12] who demonstrated these reflexes in the frog and dog. We feel that, even though we cannot at present analyze or properly interpret the curves obtained, a simple and accurate method for further study of the problem is provided.

Much of the previous experimental work along these lines has been done in an attempt to show the relationship of smooth muscle contraction to associated electrical changes; however, since the experimental procedures were different, they have little bearing on this work. Our curves are different, probably because the electrical field may be altered in experiments in which the abdomen is open.

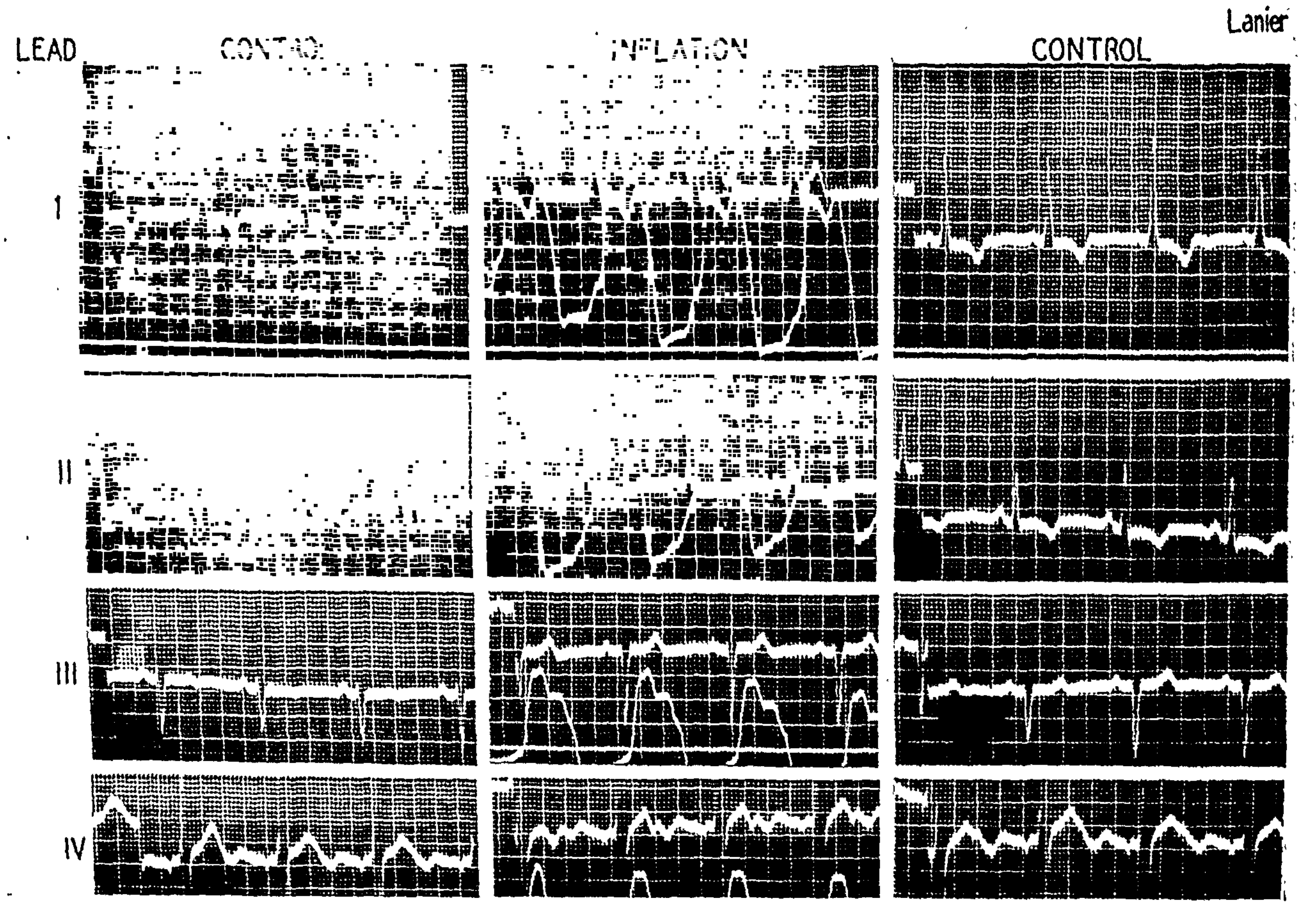

Fig. 9.—These are records of experiments similar to those shown in Figs. 6, 7, 8, and 10, except that the subject had hypertensive heart disease with myocardial changes. The blood pressure was 280/140. During distention of the stomach, note: (1) The change in the S-T segment in Lead II; (2) that the T wave of Lead III has changed to the upright position; and (3) that an extra wave has appeared in the S-T segment of Lead IV. This record also illustrates the very close relationship of the beginning of the mechanical registration of the cardiac contraction with the P wave of the electrocardiogram.

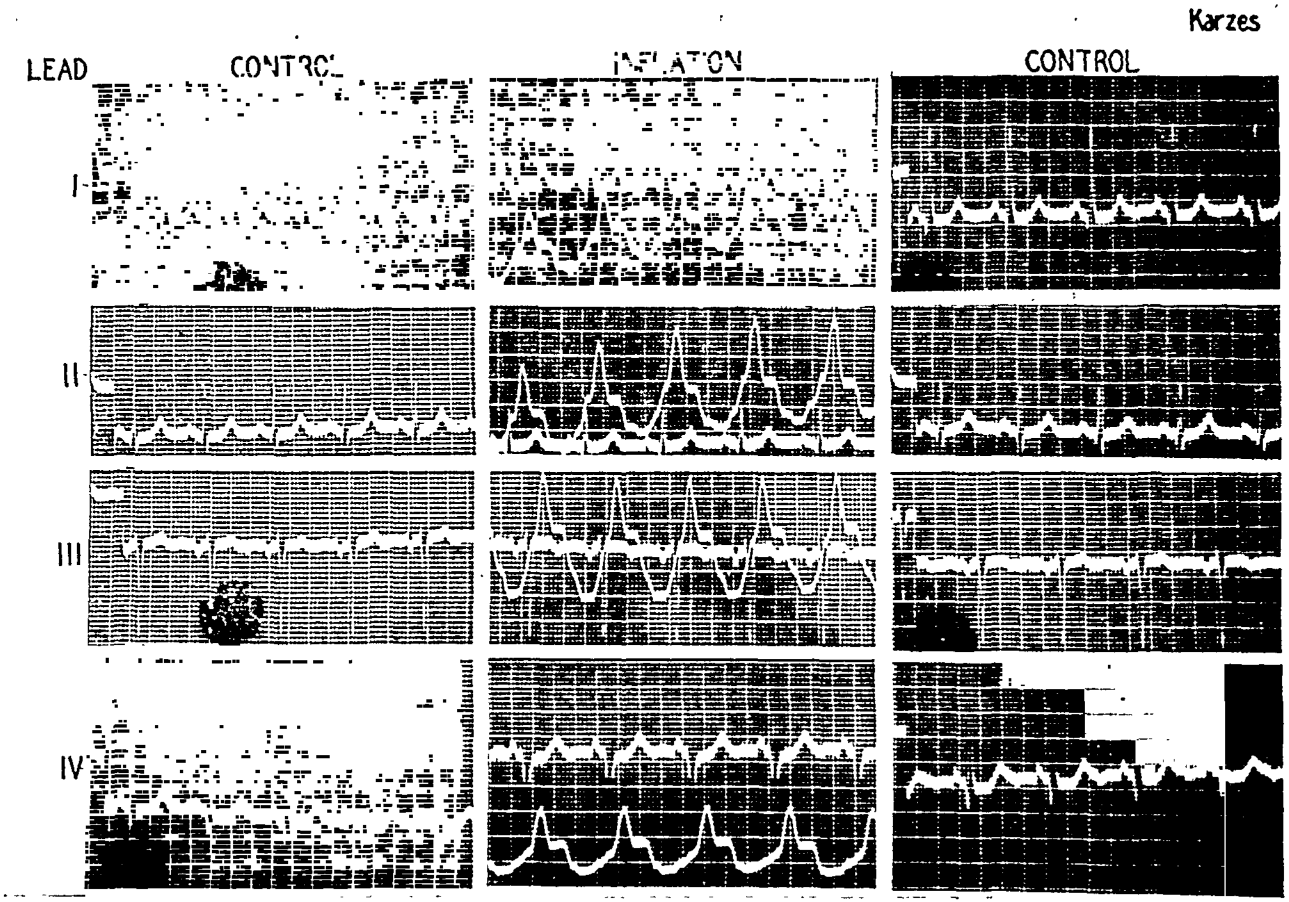

Fig. 10.—These are records of experiments similar to those shown in Figs. 6, 7, 8, and 9, except that the subject had aortic regurgitation with a blood pressure of 140/40. The most striking change in the electrocardiogram during distention of the stomach was inversion of the T wave in the third lead. This record also shows that the beginning of the mechanical registration of cardiac contraction is almost simultaneous with the P wave of the electrocardiogram.

It is of considerable interest that the cardiac component of the electrical curve obtained from the stomach and esophagus was so pronounced, in spite of the fact that the electrodes were very close together. Similar curves can be obtained with one electrode in the stomach and the other on the left wrist.

The form of the cardiac component of the electrical waves obtained from the stomach can be altered by inflation of the stomach. These alterations occur spontaneously, but particularly when the stomach is distended to the point of producing vague epigastric distress. The changes are chiefly in the S-T segment and T waves; similar changes in the standard leads are usually indicative of myocardial damage. The changes in the contour of the waves may or may not be associated with gastric hunger contractions, as recorded by the gastric balloon and electrodes.

The explanation of the marked changes which occur is not apparent at present. One cannot say whether the electrical changes are secondary to reflex activity from the stomach or to other visceral changes. On the other hand, they may be the result of an alteration of the intra-abdominal electric field caused by the introduction of a nonconductive air bubble. Some of the abnormalities may be caused by a change in the positions of the electrodes, but this cannot account for the shifting back and forth in electrograms of similar contour. Further, there is little or no correlation between the mechanograms and the electrograms which are taken from the same portion of the stomach, even in the presence of marked activity of the stomach.

The effect of distention of the stomach on the conventional leads of the electrocardiogram is a further indication of the importance of considering the possibility of the presence of a visceral factor when an electrocardiogram is interpreted. There may be a change in the position of the heart within the chest, following distention. Work done by Brams and Arens[13] showed that distention of the stomach and colon by gas increased the difficulty of percussing the heart borders accurately, whereas the teleoroentgenogram showed no change in their position. In either case, it is important to recognize that distention of the stomach in some patients may alter the form of the conventional electrocardiogram. Other extracardiac causes of changes in the electrocardiogram are alkalosis, acidosis, anoxemia, cigarette smoking, exercise, drinking ice water, stimulation of the vagus and sympathetic nerves, alteration in posture, and numerous drugs (For references, see Barker and associates[14]).

SUMMARY

A method is presented for making simultaneous mechanograms and electrograms of the stomach and esophagus.

The mechanograms are similar to those which have been described by others. The electrograms show, predominantly, the electrocardiographic type of waves. The components of these undergo spontaneous

changes, particularly following distention of the stomach. Similar curves can be obtained when both electrodes are in the stomach and when one is in the stomach and the other is applied to the left wrist. We are not able to explain the changes observed, and merely present the records to show that marked electrical variations are constantly taking place in the esophagus and stomach.

The effects of distention of the stomach on the conventional leads of the electrocardiogram are shown. In some subjects these changes were rather marked, particularly in Lead III, whereas in other subjects no changes were observed. The importance of these changes with regard to the interpretation of the standard electrocardiogram is discussed.

NOTE.—Since writing this paper, we have noted further work on this subject by Morrison and Swalm. An abstract of their work is contained in the program of the 1939 meeting of the American Medical Association. They reported changes in the electrocardiogram caused by distention of the stomach in cases of cardiac disease.

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THE PREDOMINANCE OF SURFACE OVER DEEP CARDIAC INJURY IN PRODUCING CHANGES IN THE ELECTROCARDIOGRAM*

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INTRODUCTION

FREQUENT attempts have been made to ascertain what changes develop in the electrocardiogram following injury to the heart. Injuries have been produced by ligation of coronary arteries, either at random, or as they supply specific muscle bundles, or by injection and the application of corrosives. In these studies no emphasis has been laid on the relative influence of deep and superficial injuries upon the electrocardiogram. Moreover, the irreversibility of the procedures employed would not have permitted a comparison in the same heart of injury at the two sites. In the following experiments this question was studied by a method which permits repeated observations on the same heart of the effects of both surface and deep injury.

METHODS

Seven dogs, eight cats, and two rabbits were employed. They were deeply anesthetized with sodium amytal, nembutal, or dial. While artificial respiration was being employed, the heart was exposed through the anterior chest wall, after the removal of portions of the left fourth and fifth ribs. In some experiments the pericardium was opened and sutured tightly to the chest wall to permit natural respiration. In others, the artificial respiration was maintained throughout, and the heart was permitted to rest in its natural position, usually in contact with the diaphragm and posterior muscle mass. In most experiments the animal lay on its back, but in others it lay on its right side, so that the anterior surface of the heart was in contact with the chest. The three conventional electrocardiographic leads were taken; the chest wall was closed with clips during the recording, while the lungs were expanded fully by the artificial respiration.

Surface injuries were produced by the application of small squares of filter paper soaked in M/5 and M/10 solutions of various salts. This method, employed first by Hofmann,[1] was developed as a physiologic method by one of us.[2] Heat and cold were applied by touching the surface of the heart with test tubes filled with hot or cold water. The deep musculature was injured by the injection of M/5 and M/10 KCl, in varying amounts, through a fine hypodermic needle. Precautions were taken against drying, cooling, and the accumulation in the pericardium of test solutions.

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RESULTS

A. Applications to the Surface at the Apex.—The application of isotonic sodium chloride to all parts of the surface of the heart was without effect upon the electrocardiogram. Magnesium sulfate, in the same concentration, was equally ineffective when applied to the apex. However, KCl, $CaCl_2$, and heat and cold, when applied to the apex, produced characteristic and striking alterations in the S-T portion of the complex (Fig. 1). These effects were specific for the agent employed and were consistently produced in the entire series of experiments. The changes appeared within a few seconds after the application of the agent and subsided promptly after removal of the filter paper or test tube. The effects of heat and cold disappeared most rapidly; those of the salts gradually subsided in from one to two minutes. Washing the surface of the heart after the salt applications greatly hastened the process of recovery, which was complete.

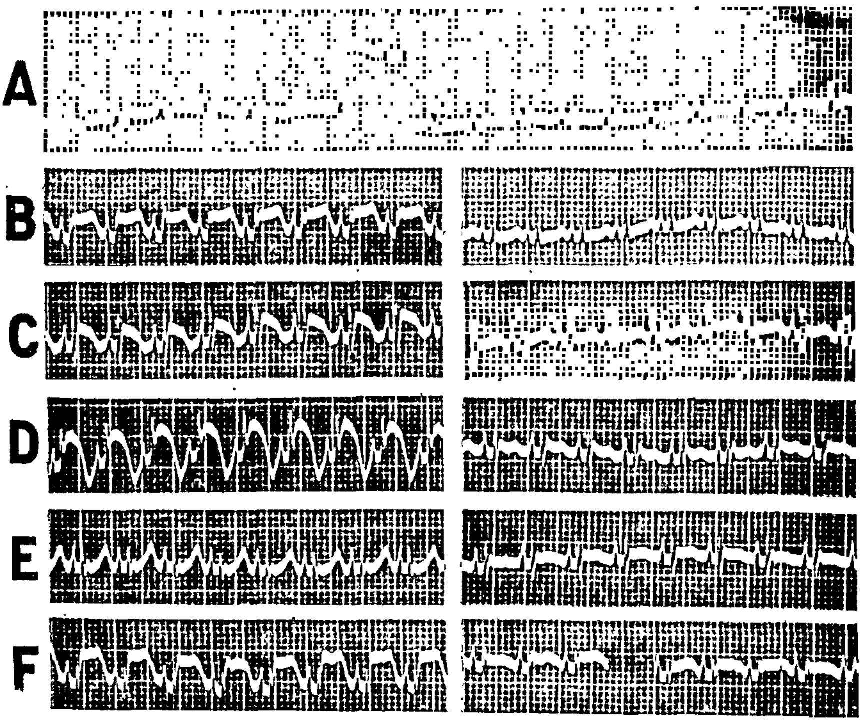

Fig. 1.—Cat, 3 kg. *A*, control, Lead II; *B*, application of M/10 KCl to apex on pledget 1 cm. square; *C*, similar application of M/10 $CaCl_2$; *D*, test tube filled with ice water applied to same region; *E*, test tube filled with hot water (60° C.); *F*, M/10 KCl just posterior and cephalad to apex. Following each record is a control from the same lead, taken from two to three minutes after removal of the application.

The magnitude of the changes was influenced by the size of the area covered by the filter paper. A piece containing about 10 mg. of the solution, covering an area of only 9 sq. mm., was sufficient, when applied to the apex, to produce a definite effect in a dog weighing 6 kg. Larger applications evoked more striking changes (Fig. 2).

B. Application to Other Surface Areas of the Ventricles.—Without exception, the most striking changes in the electrocardiogram were produced by applications to the surface at the apex. Alterations of a similar nature, but less pronounced, were produced by applications to regions along the base and the medial portion of the posterior surface. The magnitude of the alterations produced by applications to other regions depended partly upon the position of the heart in the chest. In experiments in which the heart was lifted anteriorly by suture of the pericardium to the chest wall, and was, therefore, no longer in

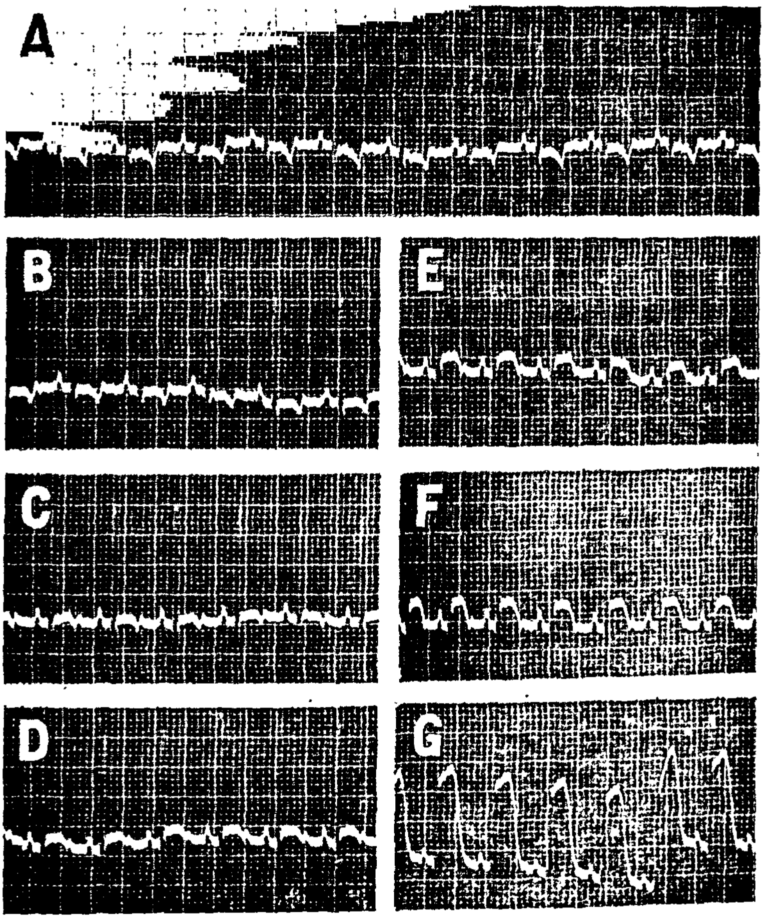

Fig. 2.—Dog, 13.5 kg. Sodium amytal anesthesia. Lead III. *A*, Control; *B*, M/5 KCl at apex, with pledget size, 0.5 × 1.0 cm.; *C*, as in *B*, with pledget size, 1.0 × 1.0 cm.; *D*, pledget 1.5 × 1.0 cm.; *E*, pledget 1.0 × 2.0 cm.; *F*, pledget 1.5 × 1.5 cm.; *G*, 1.5 c.c. M/5 KCl dropped into pericardial cavity. Controls were taken after removal of each pledget and thorough washing, and they showed complete recovery.

contact with the posterior muscle mass nor with any appreciable amount of tissue anteriorly, applications to the anterior surface produced almost no alterations. Applications to the left lateral and left posterior surfaces of the heart were also relatively ineffective, except near the base. Applications to the right lateral and adjacent anterior surfaces caused intermediate changes. When the heart was not suspended, but rested naturally in the cavity, with the lungs completely

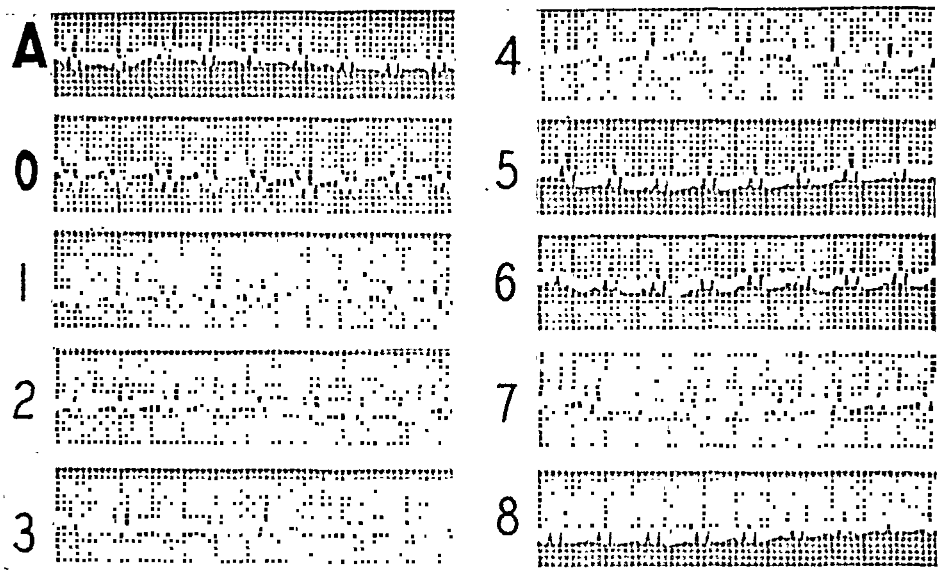

Fig. 3.—Cat, 4.7 kg. Sodium amytal anesthesia. Pericardium sewed to chest wall. Anterior surface of the heart exposed. *A*, Control, Lead II. *0* to *8*, inclusive, records following application of M/5 KCl to corresponding areas on the anterior surface. These areas are indicated in Fig. 3*A*.

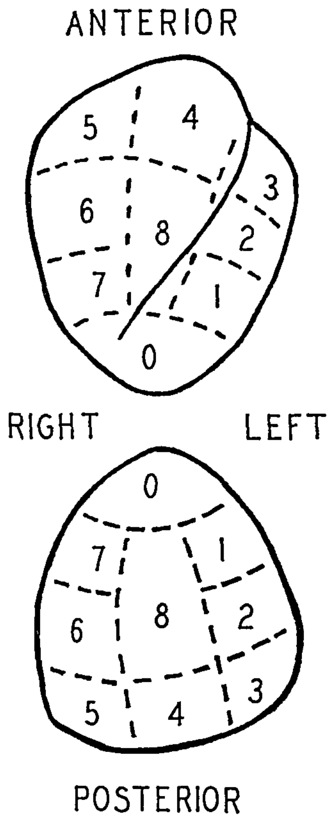

Fig. 3*A*.—Diagram indicating location of surface areas referred to in Figs. 3 to 9.

expanded around it and the posterior surface in contact with the posterior muscle mass, no posterior area was completely "silent." Applications to the entire area became much more effective than in the previous experiments, and the changes showed greater uniformity. Nevertheless, the apex retained its predominance. When the anterior surface of the heart was in contact with an intact chest wall, applications to this region became effective, but, again, injury of the apex produced greater changes (Figs. 3, 4, and 5).

When pledgets were applied to the apex, the effects of the injury were greatly diminished by proper insulation of the affected area from contact with the surrounding tissues. Unless the insulation covered an area much greater than that of the pledget, the changes were not suppressed completely.

Rubidium chloride was tested in several experiments and produced changes qualitatively similar to those evoked by KCl, but of lesser magnitude.

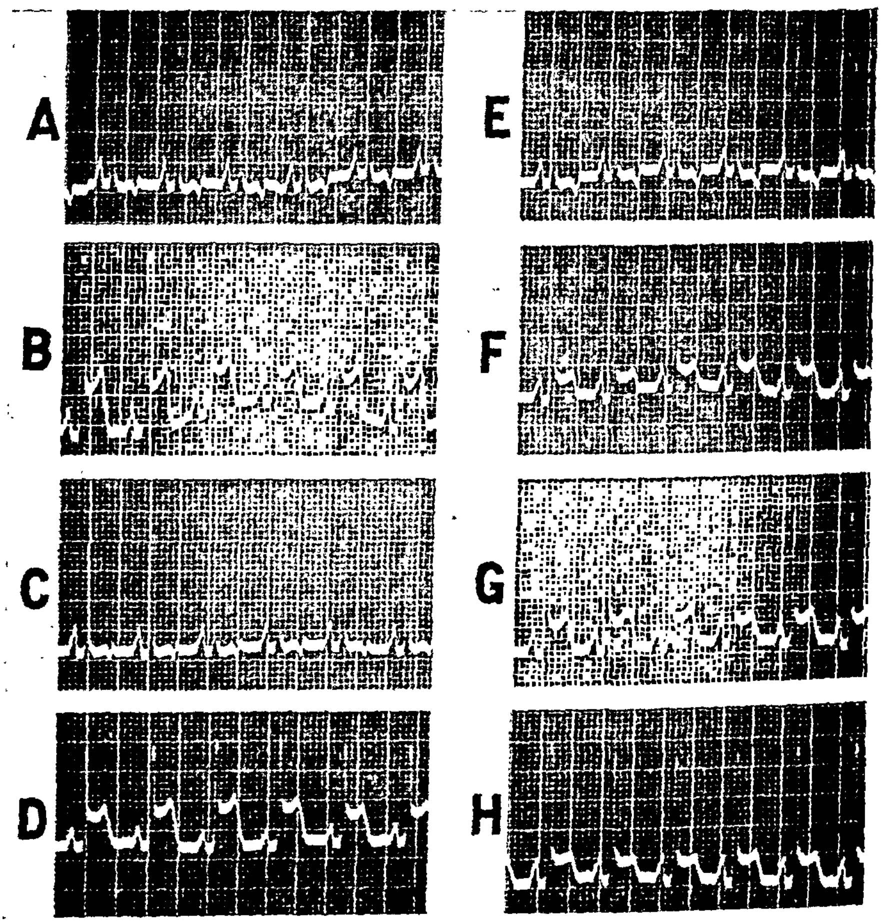

Fig. 4.—Dog, 9.1 kg. Sodium amytal anesthesia. Artificial respiration. All records taken with chest wall clipped together and lungs fully expanded. *A*, Control, Lead *II*; *B*, M/5 KCl on pledget, 1.5 cm. square, applied to area *0* (anterior); *C*, control, 3 minutes later; *D*, application of KCl to area 0 (posterior); *F*, application of KCl to area 8 (posterior); *G*, application to areas *4* and *5* (posterior); *H*, application to areas 2 and 3 (posterior). Controls were taken between applications and showed restoration to normal, as in *C* and *E*.

C. Intramyocardial Injections.—To compare the influence of surface and deep myocardial injuries, M/5 and M/10 KCl were injected intramyocardially in the region underlying the area in which the surface effects were greatest, namely, the apex. It should be emphasized that, with deep injection, some of the solution often reached the surface along the track of the needle, or infiltrated subepicardial areas, especially when volumes of as much as 1 c.c. were injected. In these instances, areas of definite loss of color marked the extent of the surface

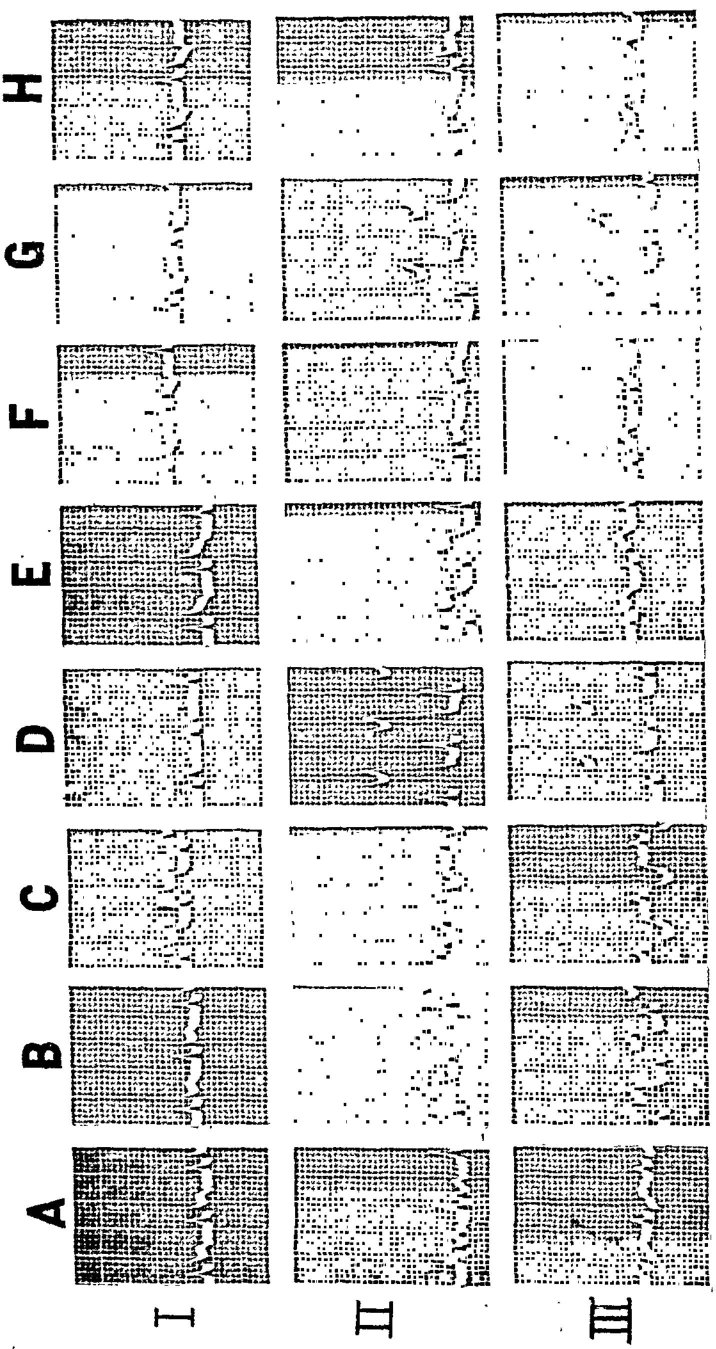

Fig. 5.—Dog, 8 kg. Sodium amytal anesthesia. Artificial respiration. Animal lying on right side, so that anterior surface of heart was almost entirely in contact with intact chest wall. *A*, Control, three leads; *B*, M/5 KCl applied to 0 (anterior) in pledget 1.5 cm. square; *C*, pledget on area 4 (anterior); *D*, pledget on area 0 (posterior); *E*, pledget on area 2 (posterior); *F*, control, 3 minutes later; *G*, pledget on area 5 (posterior); *H*, control. Controls were taken after each application, but not all of them are shown.

infiltration. A minimum estimate of the size of the area of the region affected could be made by assuming that the solution formed a sphere within the myocardium, although actually it must have been much greater. On this assumption, however, the area affected by 1 c.c. contained over 5 sq. cm., and, that by 0.1 c.c., over 1 sq. cm., which was roughly the size of the external pledget.

When the changes evoked by the application to the apex of a piece of filter paper 1 cm. square were compared with those produced by the

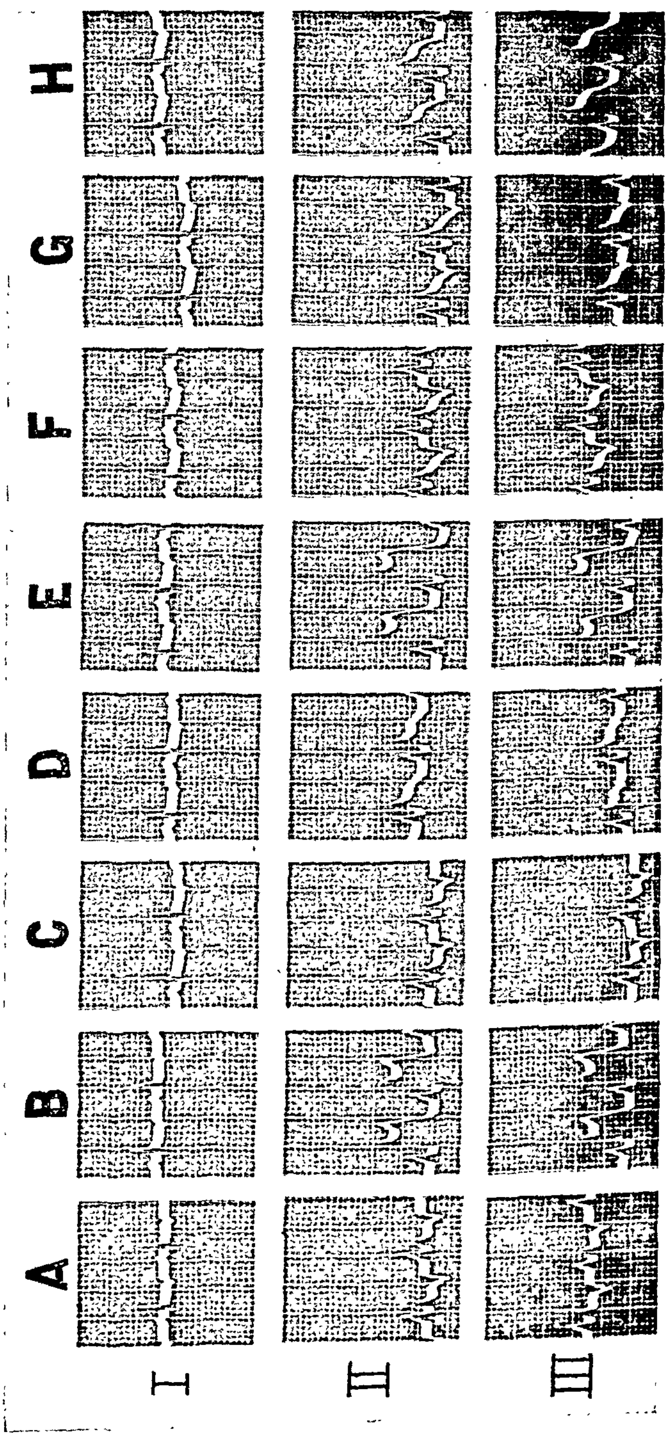

Fig. 6.—The same experiment as is shown in Fig. 4. *A*, Control, three leads; *B*, pledget (1.5 cm. square), containing M/5 KCl, applied to 0 (anterior); *C*, control, 6 minutes later; *D*, injection of 0.5 c.c. M/5 KCl into myocardium under area 0 (anterior). In *D* a small discolored area is seen. Minimum surface involved is calculated as 3 *sq. cm. E*, KCl pledget over area of discoloration; *F*, control, 2 hours later; *G*, deep injection of 0.5 c.c. M/5 KCl under 0 (posterior). *H*, KCl pledget over region injected. No superficial infiltration visible.

deep injection of even as much as 1 c.c., the surface effects were found to be much more pronounced (Figs. 6 and 7). The alterations following deep injections were not always of the same general character. In some experiments, in which the absence of surface discoloration indicated that no surface fibers were involved, and leakage around the needle track was removed by washing, almost no electrocardiographic changes were apparent. It was made certain that in these experiments the needle was not in the ventricular cavity.

In experiments in which injections near the surface produced an effect, as much as twenty minutes were required for its total disappearance. Insulation of the area greatly diminished the changes,

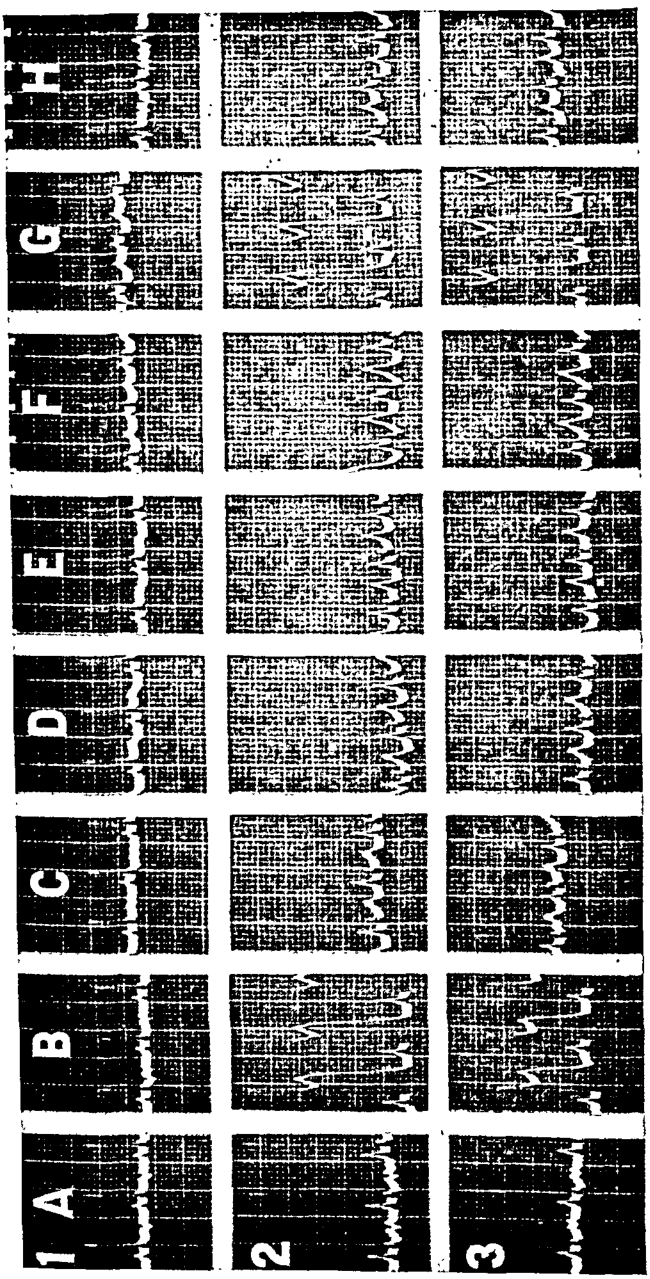

Fig. 7.—Dog, 5.5 kg. Sodium amytal anesthesia. Artificial respiration. Chest closed during recording. *A*, Control, three leads; *B*, pledget 1.0 cm. sq., containing M/5 KCl, on area 0 (posterior); *C*, control, 3 minutes later; *D*, deep injection beneath area 0 (posterior) of 0.5 c.c. M/5 KCl; *E*, second injection in same area, 5 minutes later, 0.5 c.c. M/5 KCl; *F*, third injection, 10 minutes after first, 1.0 c.c. M/5 KCl. No visible blister. *G*, Pledget over area 0 (posterior); *H*, control, 3 minutes after removal of pledget and washing.

whereas the application of a pledget produced only the change that would have occurred without the injection (Fig. 8). There was, therefore, no addition of effects. Minor changes were produced by the deep injection of NaCl solution, as well as by the presence of the needle in the myocardium. Regions other than the apex were tested with deep injections, with similar results (Fig. 9).

DISCUSSION

The application of various agents to the surface of the heart was found, in these experiments, to produce striking changes in the S-T portion of the electrocardiogram. It is significant that each agent produced a characteristic alteration which was easily distinguished and

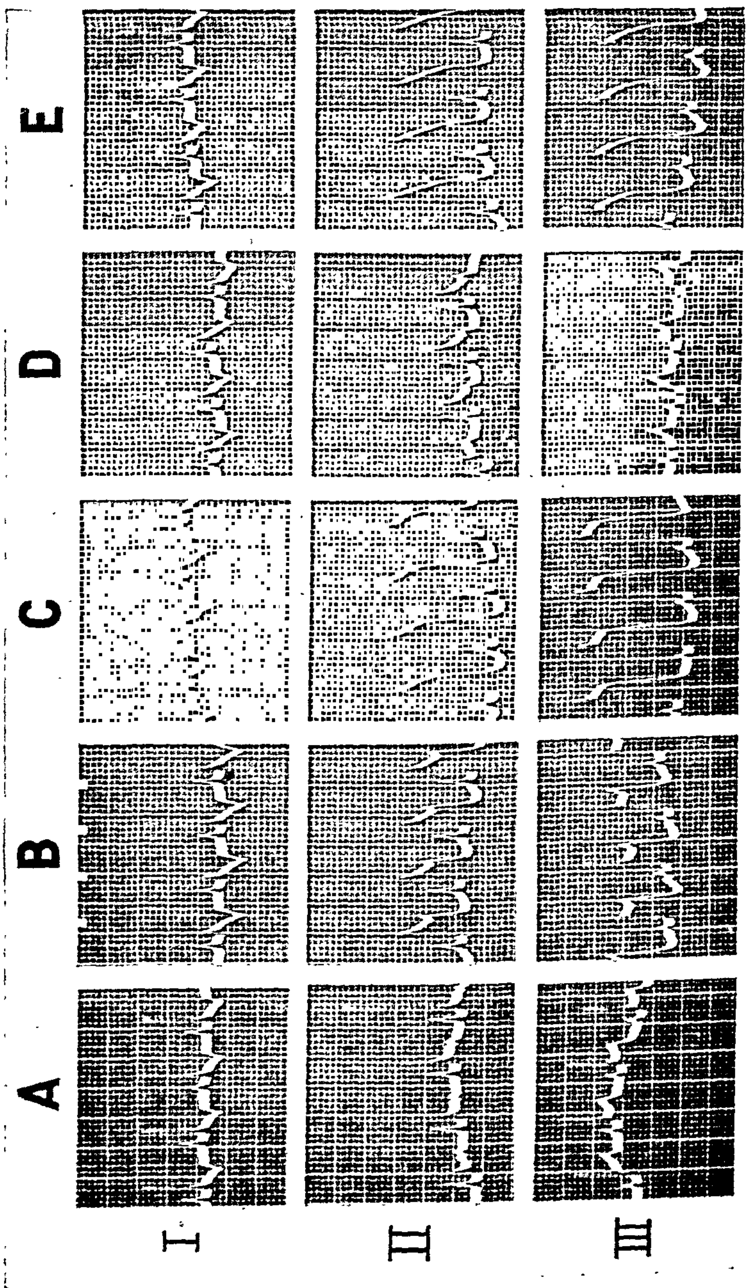

Fig. 8.—Same experiment as is shown in Fig. 5. *A*, Control, three leads; *B*, injection 1 c.c. M/5 KCl below areas 0 and 1 (posterior). Visible blister produced. *C*, Pledget over this area; *D*, insulation of this area, with pledget in place, by means of two sheets of rubber dam separated by dry cotton wool; *E*, insulation removed.

uniformly obtained. The cause of such effects cannot, therefore, be simply the paralysis of a certain number of myocardial fibers, nor can the changes be attributed to interference with the conduction of the action currents of the heart to adjacent tissues, caused by the interposition of the saturated pledget. Solutions of both potassium chloride and calcium chloride are adequate conductors, and they do not differ greatly in this respect from sodium chloride and magnesium sulfate, which were ineffective. Furthermore, the actual insulation of an affected area from the tissues usually in contact with it greatly reduced the magnitude of the changes, without altering their character.

These changes were, furthermore, rapidly and completely reversible. The changes evoked by KCl were sufficiently like those caused by $CaCl_2$ to suggest some similarity in the mechanism of the two effects.

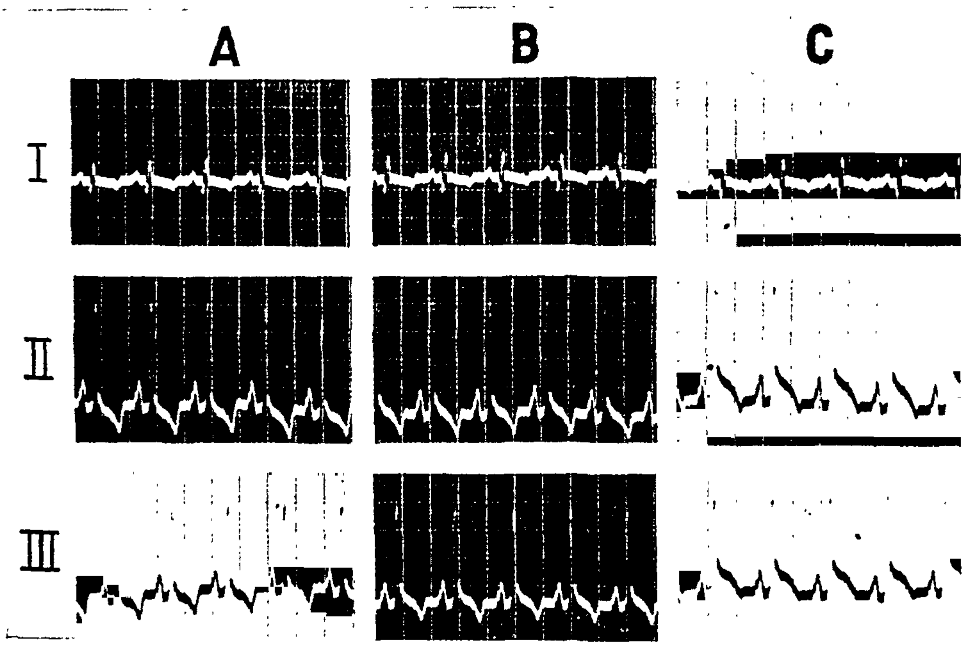

Fig. 9.—Same experiment as is shown in Figs. 4 and 6. *A*, Control, three leads; *B*, deep injection, 0.5 c.c. M/5 KCl under area 3 (anterior); *C*, KCl pledget (1.5 cm. square) applied to the same area.

When present in sufficient concentration, both substances are known to alter the activity of the myocardium, and they produce typical differences which are apparent in the contour of the S-T segment.[3, 4] The effects of heat and cold were very unlike those of calcium and potassium and were strikingly different from each other. In some respects, the effect of cold was the opposite of that produced by heat. With cold, the S-T interval became elevated and convex and the T wave sharply inverted, whereas, with heat, the T wave remained conspicuously upright.

Applications of test solutions to the surface at the apex provoked responses more striking than could be elicited from any other area of

similar size. Colombi[5] obtained similar changes by applying alcohol and other substances to the apex, but attributed them to alterations in temperature and believed that they could be obtained only at the apex. Such a preponderance of the apex does not seem to be entirely explicable in the light of what is known about surface conductivity. Katz and Korey[6] found that conduction from the apex through the diaphragm accounted for approximately 25 per cent of the potential recorded in the electrocardiogram, and that the posterior surface accounted for 40 per cent. If this be true, one would expect more striking effects from injury to the posterior surface than to the apex. With this exception, however, Katz's general concept of the importance of conduction to adjacent structures from various regions of the heart is substantiated by our results. Damage to the areas which Katz found to be ''silent'' produced, on the whole, minor alterations, whereas injury to cardiac surfaces in contact with the ''good'' conductors produced the more striking changes. Katz's view is further substantiated by the observation that adequate insulation of areas treated by applications greatly reduced or abolished the effect. This procedure followed closely that employed by Katz, except that the process was reversible. It should be emphasized, however, that, although variations in conductivity might explain the ease with which surface alterations in various regions may be detected in the electrocardiogram, it does not furnish any explanation of the mechanism of their production.

Judging from the quantities injected deeply into the myocardium, the minimum areas of injury must have been much larger than those produced on the surface. Nevertheless, the effect of superficial applications was invariably much more pronounced. In some cases, deep injections produced no changes whatever, and, in those experiments in which electrocardiographic alterations were most marked, superficial infiltration occurred and might alone have produced the effects observed. Sodium chloride solutions, and even the presence of the needle, in situ, produced some changes. It is also possible that injury to the deep layers altered either the conduction to the surface or the nutrition of the overlying areas, and thus indirectly produced surface changes. In any case, the results of superficial injury completely masked the effect of injury to deeper layers. Thus, in the presence of superficial involvement, the recognition of the existence and extent of injury to subjacent areas became impossible. It is clear, therefore, that alteration or suppression of the electrical activity at the surface is a far more potent cause of abnormality in the S-T portion of the ventricular complex than is similar involvement in the deep layers of the heart.

The classical concept presented by Einthoven, and accepted without serious question since then, stated that the electrocardiogram represents the algebraic summation of the electrical activity of all of the component fibers of the heart. It is difficult to explain by such a hypothesis the extraordinary preponderance of the effects of injury of the

surface of the heart. These experiments, moreover, afford no support to the view that the electrocardiographic changes following injury are determined by the specific contributions of individual muscle bundles. Study of single cells indicates that bioelectric phenomena occur at their surfaces. Although there is no evidence that the surface of the heart has a relation to the interior comparable to that of a cell membrane, with regard to the action potential, the experiments reported here seem to suggest such a possibility.

SUMMARY AND CONCLUSIONS

1. Application of M/5 or M/10 KCl and $CaCl_2$, and of heat and cold, to the surface of the heart produced characteristic changes in the S-T segment of the electrocardiogram which were rapidly and completely reversible. Sodium and magnesium salts were ineffective in the same concentrations.
2. The most marked changes were produced when the apex was injured. The magnitude of changes when other areas were damaged varied in accordance with their proximity to conducting structures.
3. Injections of KCl into the deeper layers of the heart produced relatively minor changes, or none at all.
4. Changes in the S-T segment of the electrocardiogram betray injuries to the surface of the heart with far greater effectiveness than injuries to the deeper layers.
5. The effects of surface injuries completely mask those of damage to subjacent regions.
6. The magnitude of the electrocardiographic changes following injury to the heart are almost entirely conditioned by the nature, extent, and location of surface involvement.
7. It is possible that the electrical activity of the ventricles is a phenomenon which is determined largely by the surface of the heart.

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THE RELATION BETWEEN BUNDLE BRANCH BLOCK AND CARDIAC ENLARGEMENT

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THE conception of bundle branch block in man is dominated almost entirely by the pioneer researches on animals of Eppinger and Rothberger,[1] and Lewis,[2] who produced a characteristic type of electrocardiogram by sectioning the right or left branch of the A-V bundle. Such an electrocardiogram shows left or right axis deviation, prolongation of the QRS complex beyond 0.12 second, with notching, and T waves pointing in a direction opposite to that of the main deflections of the QRS complexes.[3] The chief controversy has concerned the type of electrocardiogram which corresponds to a lesion in the right or left bundle branch. It is now generally agreed in this country that a block in the left bundle branch results in left axis deviation, and a block in the right bundle branch, in right axis deviation.[4-9]

While we accept the view that a lesion of a bundle branch produces a specific bundle branch block pattern, for example, in acute conditions like coronary artery occlusion[10] and rheumatic fever, we believe that in the majority of chronic cases the anatomic basis of this electrocardiographic pattern is diffuse myocardial damage probably involving both bundle branches, and enlargement of one or the other of the ventricles. We have been impressed with the frequent occurrence of cardiac enlargement, usually of marked degree, when bundle branch block is present. Furthermore, we have found that left bundle branch block is usually associated with enlargement of the left ventricle, and right bundle branch block with that of the right ventricle. We believe that these relationships are causal, not fortuitous, a view which has been hinted at infrequently in the past.[11-15]

MATERIAL

The material for this study consisted of the last 100 consecutive cases of bundle branch block at the Mount Sinai Hospital, in all of which the size of the heart was ascertained at necropsy or by means of teleoroentgenograms or fluoroscopic examination. There were fifty-nine men and forty-one women; their ages ranged from 11 to 77 years. Etiologically, the cases fell into four groups: coronary arteriosclerosis, with or without hypertension, fifty-eight cases; coronary artery occlusion, twenty-five cases; chronic rheumatic cardiovalvular disease, 9 cases; miscellaneous conditions, 8 cases, including von Gierke's disease, syphilis, Graves' disease and congenital heart disease. Three of the patients

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with Graves' disease were over 45 years of age; therefore, coronary sclerosis may have been present. Thus, it is seen that arteriosclerotic heart disease, including coronary occlusion, accounted for 86 per cent of the cases. Such a high incidence has been noted also by others.[15-17]

Only electrocardiograms showing the typical pattern of bundle branch block, with a QRS interval which measured at least 0.12 second, were accepted for study. High voltage was not considered requisite; in fact, the voltage was normal in the majority of cases. Atypical records, for example, those in which there were both left axis deviation and a large S wave in Lead I, were excluded. Left bundle branch block was present in 90 per cent of the cases, and right bundle branch block in 10 per cent, which is a somewhat higher ratio of left bundle branch block than that usually reported.[15-18] In five cases which were included in the series, complete A-V dissociation was present in addition to the bundle branch block; the latter was left-sided in four, and right-sided in one.

The heart was regarded as enlarged if it weighed 375 Gm., or more, at necropsy, or if it appeared enlarged in the teleoroentgenogram. The cases have been divided into two groups, depending upon whether the size of the heart was ascertained after death or during life.

Death occurred in thirty-one cases; in twenty-eight of these the heart was examined at necropsy and found to be almost invariably increased in size (Table I). The average cardiac weight was 586 Gm. In eighteen

TABLE I

TYPES OF BUNDLE BRANCH BLOCK AND HEART WEIGHTS IN THE VARIOUS KINDS OF HEART DISEASE (POST-MORTEM CASES)

ETIOLOGY	NUMBER OF CASES	BUNDLE BRANCH BLOCK		HEART WEIGHT			
		LEFT	RIGHT	600 GM AND OVER	500-599 GM.	400-499 GM.	375-399 GM.
Coronary sclerosis and/or hypertension	7	7	0	1	2	2	2
Coronary occlusion	14	11	3	2	6	6	0
Rheumatic chronic cardiovalvular disease	4	3	1	3	1	0	0
Miscellaneous	3	3	0	2	1	0	0
Total	28	24	4	8	10	8	2

cases the heart was very large; it weighed 600 Gm., or more, in eight, and from 500 to 599 Gm., in ten. In eight cases the weight was between 400 and 499 Gm. In the two remaining cases the heart was only slightly enlarged, weighing between 375 and 399 Gm.; it is noteworthy that these patients succumbed to extracardiac disease. Each of the four etiological groups contributed some of the largest hearts, but the average cardiac weight in the cases of coronary artery occlusion was only 530 Gm., whereas that in the hypertensive arteriosclerotic group was 649 Gm.

In the remaining seventy-two cases the heart was examined roentgenologically (Table II). It was enlarged in all but six cases of left bundle branch block; when right bundle branch block was present, the heart was always enlarged. In twenty-nine cases the degree of enlargement was marked, and in twenty-nine it was moderate. In eight cases the increase in size was slight. In three of the cases in which there was little or no enlargement, the clinical diagnosis was thyrotoxicosis, and the conduction defect may have been functional; however, the possibility of coronary sclerosis could not be excluded.

In Tables III and IV the type of bundle branch block, left or right, is correlated with preponderant left and right ventricular enlargement. In some cases in which both ventricles were increased in size it was impossible to say which was the larger. We have also excluded the five cases of complete A-V block. It will be seen (Table III) that the left ventricle was definitely larger than the right in 71 per cent of the cases of left bundle branch block, and that in no case of left bundle branch block was the right ventricle preponderant. It is significant that hypertensive arteriosclerotic heart disease, which produces left ventricular enlargement, was associated with left bundle branch block in all but one case, in which complete A-V dissociation was also present (Tables I and II, Fig. 1). There were four cases of rheumatic heart disease with left bundle branch block, and in three of these aortic valvular disease was present.

Of the ten cases of right bundle branch block (Table IV), the right ventricle was larger than the left in four and the left ventricle was preponderant in one. In five of the ten cases of right bundle branch block the lesion was caused by rheumatic heart disease; in four, as a result of advanced mitral stenosis, the right ventricle was preponderant over the left (Fig. 2). In the fifth case, in which aortic stenosis and insufficiency, as well as mitral stenosis, were present, the left ventricle was larger than the right. In addition, the coronary arteries were sclerotic and very narrow; this may explain the presence of right bundle branch block, for it is possible that the artery supplying the right branch was occluded. The remaining five cases were instances of coronary artery occlusion. In only one of these was the right ventricle actually larger than the left; in the remaining four both ventricles were enlarged. It appears that in cases of coronary artery occlusion the location of bundle branch block may not depend entirely upon ventricular enlargement, but also upon whether there is infarction of the septum which interferes with conduction through one of the branches.[10] One of the five patients with A-V dissociation had right bundle branch block, yet the left ventricle was preponderant over the right.

A microscopic examination of the ventricular muscle was made in every case in which an autopsy was done, but there was no specific

attempt to investigate the bundle branches. Ventricular abnormalities, that is, fibrosis, infarction, or glycogen infiltration (in the case of von Gierke's disease), were present in all cases, and were, as a rule, generalized.

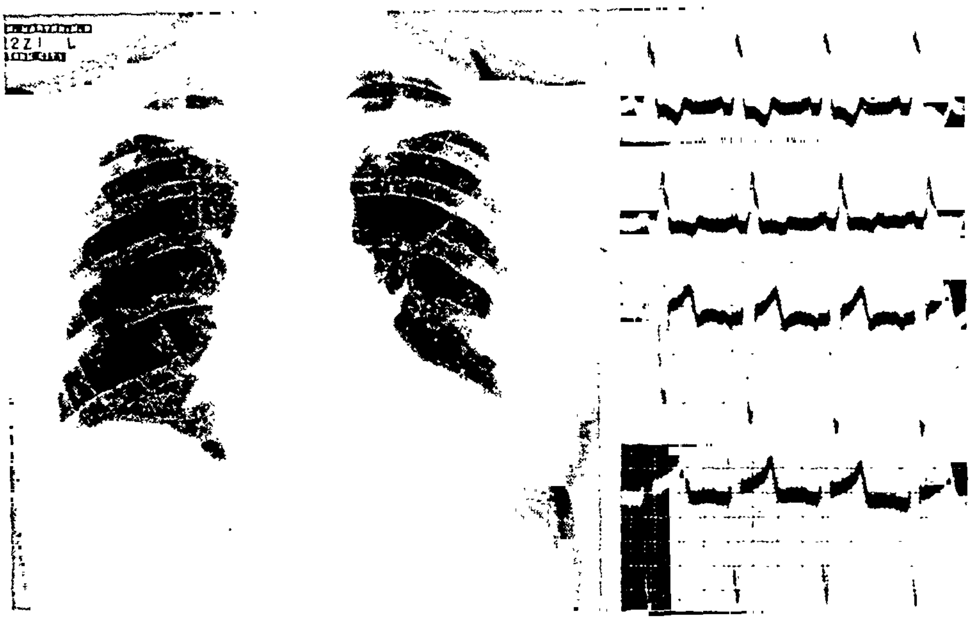

Fig. 1.—S. B., male, 68 years old. Long-standing hypertension, blood pressure 170/110, angina pectoris. No history of coronary occlusion or heart failure. Electrocardiogram shows typical left bundle branch block. Teleoroentgenogram reveals very marked enlargement of the left ventricle.

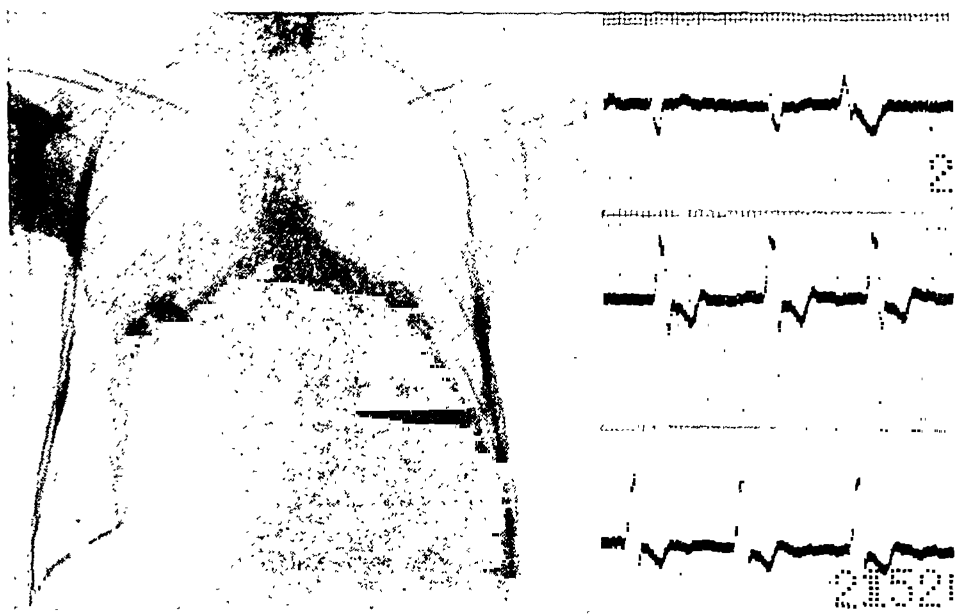

Fig. 2.—F. P., male, 44 years old. Chronic rheumatic valvular disease, with involvement of mitral, aortic, and tricuspid valves. Auricular fibrillation and congestive failure were present. The electrocardiogram shows right bundle branch block. The teleoroentgenogram shows enlargement of the right and left ventricles. At necropsy the right ventricular enlargement was predominant.

TABLE II

TYPES OF BUNDLE BRANCH BLOCK AND HEART SIZE IN THE VARIOUS TYPES OF HEART DISEASE (EXCLUDING POST-MORTEM CASES)

ETIOLOGY	NUMBER OF CASES	BUNDLE BRANCH BLOCK		CARDIAC ENLARGEMENT			
		LEFT	RIGHT	MARKED	MODERATE	SLIGHT	NORMAL
Coronary sclerosis and/or hypertension	51	50	1	21	21	6	3
Coronary occlusion	11	9	2	5	6	0	0
Rheumatic chronic cardiovalvular disease	5	1	4	1	2	2	0
Miscellaneous	5	5	0	2	0	0	3
Total	72	65	7	29	29	8	6

TABLE III

HEART SIZE AND PREPONDERANT VENTRICULAR ENLARGEMENT IN LEFT BUNDLE BRANCH BLOCK

HEART SIZE	NUMBER OF CASES	PREPONDERANT VENTRICULAR ENLARGEMENT		
		LEFT	RIGHT	INDETERMINATE
Cases in Which Death Occurred (Autopsy)				
600 Gm. and over	6	4	0	2
500-599 Gm.	7	6	0	1
400-499 Gm.	4	2	0	2
375-399 Gm.	2	1	0	1
Definite enlargement	2	0	0	2
Cases in Which Death Did Not Occur (X-ray)				
Marked enlargement	26	21	0	5
Moderate enlargement	26	21	0	5
Slight enlargement	6	5	0	1
No enlargement	6			
Total	85	60	0	19

TABLE IV

HEART SIZE AND PREPONDERANT VENTRICULAR ENLARGEMENT IN RIGHT BUNDLE BRANCH BLOCK

HEART SIZE	NUMBER OF CASES	PREPONDERANT VENTRICULAR ENLARGEMENT		
		LEFT	RIGHT	INDETERMINATE
Cases in Which Death Occurred (Autopsy)				
600 Gm. and over	2	1	0	1
500-599 Gm.	1	0	1	0
400-499 Gm.	1	0	0	1
Cases in Which Death Did Not Occur (X-ray)				
Marked enlargement	2	0	1	1
Moderate enlargement	2	0	0	2
Slight enlargement	2	0	2	0
Total	10	1	4	5

DISCUSSION

Our observations make it evident that ventricular enlargement and myocardial disease are almost constantly present when the electrocardiogram shows bundle branch block. Enlargement was present in almost every case in which death occurred, and in 94 per cent of the entire series; its degree was marked or moderate in 83 per cent. Cardiac enlargement has been present, also, in the majority of cases reported by other authors;[15-18] the percentage has varied from 74 to 93. In some of these, the presence of enlargement was established by percussion only; it is possible, therefore, that enlargement was actually more frequent.

The importance of cardiac enlargement is further emphasized by the fact that the type of bundle branch block is determined usually by the ventricle that is enlarged. This correspondence was very evident in our series; in no case of left bundle branch block was the right ventricle preponderant, and in only one case of right bundle branch block uncomplicated by complete A-V dissociation was the left ventricle proportionately larger than the right. It is noteworthy that conditions which produce enlargement of the left ventricle, such as hypertension and arteriosclerosis, usually are associated with left bundle branch block (Fig. 1), and diseases resulting in right ventricular enlargement, such as mitral stenosis, with right bundle branch block (Fig. 2). In our series the bundle branch block was left-sided in almost 100 per cent of the patients with hypertension and arteriosclerosis; others[15, 18, 19] have reported that this was true in approximately 80 per cent of their cases. Bayley[15] observed that patients with mitral stenosis developed right bundle branch block because the right ventricle was under strain and enlarged. Since enlargement of the left ventricle is much more common than enlargement of the right, left bundle branch block is the type usually encountered.

A number of pathologic observations confirm our belief that bundle branch block is related to cardiac enlargement and diffuse ventricular damage, and not alone to an isolated break in the continuity of a bundle branch. Bach[11] pointed out that, despite innumerable microscopic sections, in the majority of the cases of bundle branch block which have been reported no lesion was found to indicate that there was a complete structural alteration in the conducting system, as distinguished from the myocardium as a whole.[20] Furthermore, the involvement of the bundle branches is usually bilateral;[5, 9, 20, 21] this is inconsistent with the fact that either left or right bundle branch block may occur alone. Another point against the theory that an isolated bundle branch lesion alone is the cause of bundle branch block is the fact that left bundle branch block is much more common than right. Since both bundle branches are supplied by the left coronary artery, the two types should be equally common. It would thus seem that the changes in

the bundle branches are merely a part of the generalized ventricular disease, and that an additional factor is necessary to produce actual bundle branch block. This factor is cardiac enlargement. The myocardial disease, including involvement of the bundle branches, produces the intraventricular conduction defect, but the character of the ventricular enlargement determines whether the bundle branch block will be left-sided or right-sided.

One of us[22, 23] has shown that enlargement of a ventricle often produces marked changes in the electrocardiogram; for example, when the left ventricle is enlarged as a result of hypertension or aortic valvular disease, the electrocardiogram is characterized by left axis deviation, high voltage of the QRS complex, depression of the R-T segment and inversion of the T wave in Leads I and II. This pattern resembles that of left bundle branch block, except that the QRS interval is of normal duration. As fibrosis of the myocardium becomes widespread in the enlarged chamber, the QRS complex may become widened and notched, and this not infrequently leads to the typical pattern of bundle branch block. We have observed several cases in which such a transformation took place in the absence of coronary occlusion, and other authors have reported a similar experience.[11, 13] Presumably, the only change in the heart was an increase in the size of the left ventricle and in the degree of myocardial involvement. It is even possible that bundle branch block may occur in a large heart in the absence of myocardial disease. Although the latter was present in all of the cases in our series in which necropsy was performed, Pardee and Price[24] reported two instances of very large hearts without morphologic changes in which bundle branch block was present.

The mechanism by which enlargement of a ventricle aids in producing bundle branch block probably depends, as Fahr[4] suggested, upon an increase in the length of the conduction pathway in that ventricle, which delays conduction of the impulse through that ventricle as compared to the smaller one. As a result, the electrical balance between the two ventricles is upset. The use of the monocardiogram has confirmed this idea, for Mann[6] has shown that in bundle branch block the electrical path is in the same direction as in an enlarged ventricle; the only difference is that the length and irregularity of the pathway are increased.

We believe that sufficient evidence has been presented to indicate that chronic bundle branch block need not always be attributed to a localized lesion in a bundle branch. That interference with conduction in a bundle branch may produce a bundle branch block pattern has been shown experimentally, as well as in the rare instances of gumma of the bundle and the occasional cases in which a functional type of block occurs in normal hearts. It may also explain the bundle branch block which occurs during heart failure and in the course of acute diseases, such as rheumatic fever and coronary artery occlusion. It should

be noted, however, that even in cases of coronary artery occlusion, cardiac enlargement plays a role, for we found that left bundle branch block was much more common than right, and coronary artery occlusion usually occurs in hearts which have large left ventricles. Since each bundle branch is supplied by branches of the right and left coronary arteries, and since these are occluded with equal frequency, one would expect the incidence of right and left bundle branch block to be the same, unless there were another factor, such as cardiac enlargement.

SUMMARY

The size of the heart was ascertained at necropsy or by roentgenologic examination in 100 consecutive cases of typical bundle branch block.

The clinical diagnoses were: arteriosclerotic heart disease, 58 per cent; coronary artery occlusion, 25 per cent; chronic rheumatic valvular disease, 9 per cent; and miscellaneous conditions, 8 per cent.

The heart was enlarged in all cases in which it was examined post mortem; the average cardiac weight was 586 Gm., the lowest, 375 Gm.

Of the cases in which there was only a roentgenographic examination, the heart was increased in size in 91 per cent. In three of the six cases in which there was no enlargement, the diagnosis was Graves' disease.

Left bundle branch block was present in 90 per cent of the cases. In 71 per cent of these the left ventricle was larger than the right, and in none was the right ventricle preponderant. Hypertensive heart disease was almost invariably associated with left bundle branch block.

Of the ten cases of right bundle branch block, the right ventricle was predominant in four, and the left ventricle in one. Both ventricles were enlarged in five cases of coronary artery occlusion.

Diffuse myocardial involvement was found in all cases in which a necropsy was performed.

It is concluded that, in most instances, chronic bundle branch block is the result of an increase in the size of the heart, and of myocardial damage, with diffuse involvement of the bundle branch system. The type of bundle branch block depends on which ventricle is predominantly enlarged.

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THE EXAMINATION OF THE HEART AND LUNGS BY THE CARDIOCAIROGRAPHIC METHOD

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FOR years, attempts have been made to make roentgenographic exposures of the chest at a predetermined phase of the cardiac cycle, by synchronization of the exposure with heart sounds, pulse waves, or action current impulses. The methods which utilize the carotid pulse[1] or the heart sounds (Rivolta) suffer from an inherent difficulty, in that both the heart sounds and the pulse waves occur during systole, and, in order to synchronize the exposure with the end phase of diastole (the desirable instant, as will be shown later), it becomes necessary to introduce a delay, the magnitude of which depends upon the pulse rate. Since this may be variable even in the same person, no uniform results can be expected, for the adjustment for pulse rate cannot be exact. Further, the interference produced by extraneous noises and the variable quality of the first and second sounds are additional difficulties which cannot be overcome in the heart-sound method.

The action current of the heart has been used as a control, by timing the disturbance produced by the roentgen exposure on simultaneously recorded electrocardiograms, or by using the action currents of the heart to set off the exposure (Bergk and Chantraine[2]). The method here described also makes use of the action currents of the heart,[3] but by means of a special, but simple, circuit which has no inherent delay or lag. The R wave of the electrocardiogram is utilized to set off the circuit-closing mechanism which makes the roentgenographic exposure, because correlation of the roentgenkymographic movement wave with electrocardiographic phenomena has shown that the peak of the R wave is attained about 0.08 second before the beginning of the systolic movement, and that it therefore corresponds to the time of maximum diastole, that is to say, to the end of the period during which the musculature of the ventricle is expanding.

The apparatus herein described was designed and constructed by Myron Schwarzschild.[3] It closes the circuit of the x-ray machine at the moment when the R wave is at its peak, or shortly thereafter, and thus produces a roentgenogram of the heart during the period of maximum diastole. By inserting a delay mechanism in the circuit, the x-ray exposure may be made at the instant when the heart is in maximum systole. The apparatus is called the cardiocairograph, from the Greek word "kaipoσ" (kairos), meaning a definite point of time; the letter c is substituted for k in order to avoid confusing "cairograph" with "kymograph."

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The interval between the peak of the R wave and the period of maximum systole is relatively constant, namely, about 0.20 second, and it is relatively independent of the pulse rate.

Fig. 1 illustrates the plan of the apparatus. The electrocardiographic leads from the patient are connected to an amplifier which is equipped with a special cathode-ray tube (the ''Magic Eye,'' a cathode-ray type of thermionic vacuum tube, Type 6E5, such as is used in many radio receivers as a visual tuning indicator). The indicator of the tube is in the form of a fluorescent-lighted sector which covers the whole area of the target, and is viewed through the top of the bulb. During the operation of the tube, the two edges of the lighted portion separate with a fanlike motion, leaving an unilluminated sector on the conical plate. This tube enables the operator to watch the action currents and to select the lead most suitable for the purpose, namely, the lead which has the largest R deflection. Should there be inversion of the deflection in the lead which is selected, it is shown in the cathode-ray tube, the leads are accordingly interchanged simply by throwing a switch arranged for that purpose.

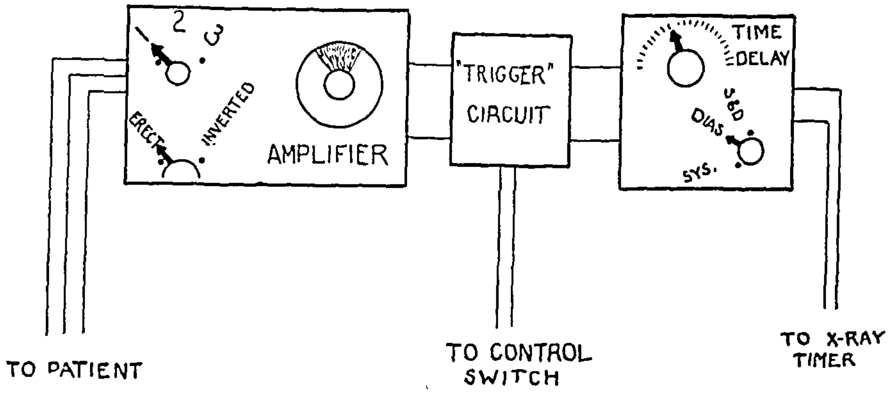


Fig. 1.—The plan of the cardiocairograph.

The output of the amplifier, which is about ten thousand times greater than the input voltage, is fed into a ''trigger'' circuit. The essential elements of the trigger circuit are a thyratron tube and a condenser. The thyratron tube is a gas-filled triode in which the plate-to-cathode path is open as long as the grid potential is maintained below a certain fixed level; if the grid potential is raised, even momentarily, above this fixed level, the plate-to-cathode path becomes conducting and remains so until the external plate circuit is interrupted. Fig. 2 illustrates the course of events about to be described. With the patient connected and the amplifier operating, the amplified electrocardiographic waves are impressed upon the grid of the thyratron in such a manner that the peaks never reach the flashover potential referred to above. When the control switch is closed, two things occur. First, the plate circuit of the thyratron tube is completed; and, second, a condenser, which up to this time has been charged and has depressed the grid potential, begins to discharge. The grid potential thus rises, as indicated in Fig. 2, and the thyratron tube flashes over at the instant the grid attains the flashover potential. A consideration of Fig. 2 shows that this obviously must occur near the peak of the ascending limb of the R wave.

The flashover phenomenon in the thyratron tube permits current to flow in the plate circuit of that tube. This circuit includes a delay mechanism and the roentgen timer (Fig. 2). The delay mechanism is equipped with a three-point switch which is so arranged that, in the systolic position, a predetermined delay, usually 0.20 second, is introduced between the flashover and the closing of the roentgen contactor. In the diastolic position, the delay device is out of the circuit, and the flashover of the thyratron tube causes the immediate activation of the roentgen circuit. In

the third position, two roentgen exposures are made, one directly actuated by the flashover, and the other at a predetermined time (0.20 second) thereafter.

It is thus possible to make exposures either in systole or in diastole, or, if desired, to make two exposures on one film to show the difference in the cardiac shadow during the two phases.

In some cases the R wave does not extend above the T wave in any lead. For this reason, the amplifier is so arranged that the rapid R deflections are amplified to a much greater degree than the slower waves of the electrocardiogram. Therefore, the potential variations reaching the thyratron grid are not a true magnification of the electrocardiogram, but rather a distorted representation in which the important R waves are highly magnified and the undesirable P and T waves are relatively suppressed. The time of the R wave is, however, unchanged.

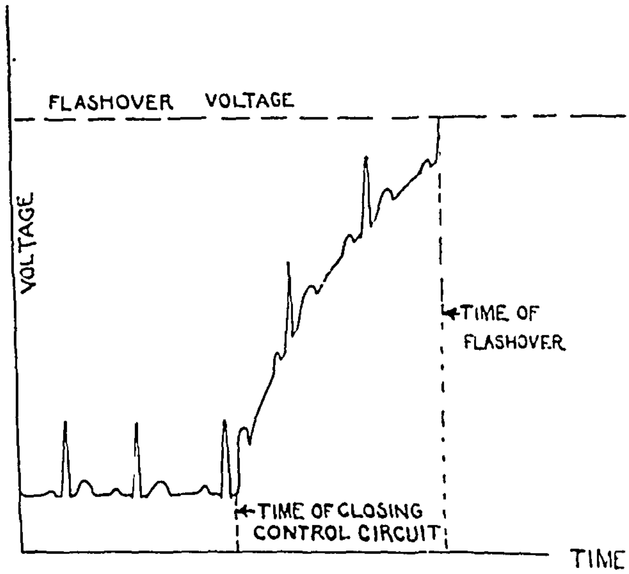


Fig. 2.—The course of the potential variation of the grid of the thyratron tube during the period just preceding the roentgen exposure.

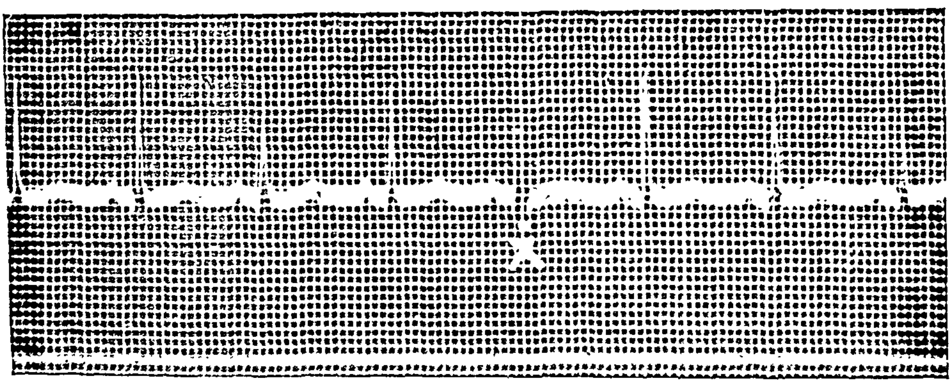
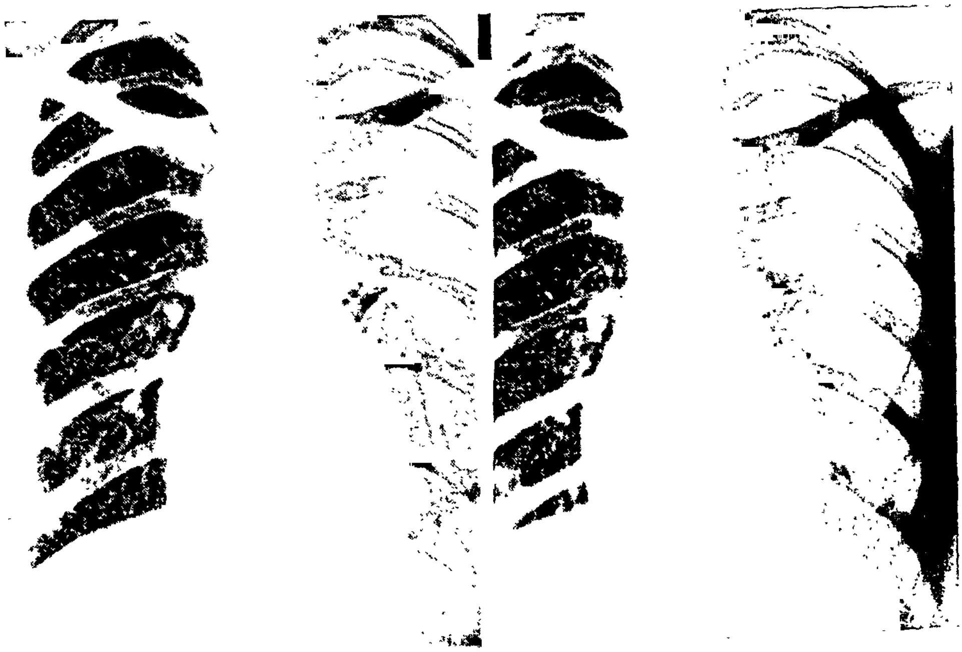


Fig. 3.—An electrocardiogram taken on a patient simultaneously with a cardiocairogram. A break in the electrocardiographic tracing is noticed at X, which corresponds to an R wave, showing that the cardiocairograph, when used without the delay device, actually makes the roentgen exposure at the time of the R wave.

For the satisfactory operation of this apparatus, the timing device of the x-ray machine and its associated mechanism must have an extremely rapid response. Ordinary timers are unsatisfactory because their latent periods vary from one-thirtieth to one-quarter of a second.

To prove that the cardiocairograph accomplishes the purpose for which it was designed, an electrocardiogram was made with a string galvanometer on a subject who was simultaneously connected with the cardiocairograph (Fig. 3). The point marked X indicates the time at which high tension was applied to the roentgen tube, since at that moment the string of the galvanometer was thrown off the field by the induced voltage from the roentgen tube leads. It is to be noted that the roentgen exposure took place before the downstroke of the R wave.

By utilizing a cathode-ray oscillograph with a lag screen, a fluorescent image of the electrocardiogram may be produced, upon which the point of roentgen exposure is clearly indicated. For this purpose, one pair (vertical) of deflecting plates is connected to the amplifier output, and the other is connected to a slow-sweep circuit which moves the beam across the screen at a speed of about 1 inch per second.



A. *B.*

Fig. 4.—Cardiocairographic exposure of the thorax to demonstrate exact reduplication of the cardiac contour. An interval elapsed between the exposures, and the slight variation in the respiratory phase has slightly varied the relative position of the pulmonic markings.

To prove that the moments selected for the exposure are really diastolic and systolic, respectively, checks were made on a number of subjects, using the kymogram as a control. The cardiocairograph was arranged to initiate the kymographic exposure during maximum diastole in one series, and, in another series, to begin the exposure during maximum systole. Fig. 5*A* shows a kymographic exposure during maximum *diastole*. It will be noted that along the ventricular border the beginning of each band is actually at the point of maximum diastole. In Fig. 5*B* the kymographic exposure was made during maximum *systole*.

The method here described for making kymographic exposures at a definite phase of the cardiac cycle, as determined by the action current phenomenon, may be utilized with kymography. In these cairokymograms, as such films may be called, the wave motion begins at the same definite point in the cardiac cycle in the bands of different films.

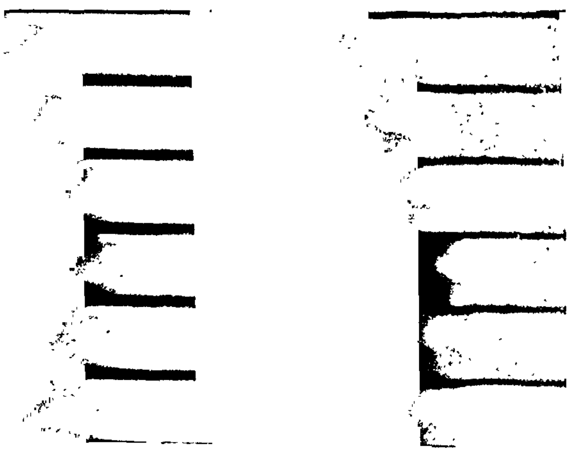
In studying kymograms in the past, it has always been necessary to correlate the beginning of ventricular systole with the beginning of the outthrust of the vascular

wave, and the end of ventricular systole with the sound notch of the vascular wave. In kymograms in which these waves or notches are not well defined, the cairokymogram would facilitate orientation.

APPLICATION

The application of this method of making roentgenographic exposures of the chest is twofold: (1) It is of value in the establishment of normal standards for the cardiac shadow, and (2) in the attainment of maximum detail and sharpness in the pulmonary roentgenogram.

1. It is high time that roentgenograms of the heart were made, and designated as being made, either during ventricular systole or ventricular diastole. This is important, first, because it is necessary to know the normal contour of the cardiac shadow, and, second, because we must have standards for mensuration. Inasmuch as mensuration of the cardiac shadow as a diagnostic method will continue to be used, and since standard tables of cardiac measurements will be constructed and reconstructed, it is important that we know whether the cardiac shadow which is measured is that during systole, or diastole, or both. Kymographic examinations have shown that there may be a difference of from 1 to 2 cm. in the transverse or long diameter of the cardiac shadow, depending on whether the exposure was made during systole or diastole. Further, if the effects of various therapeutic measures are to be judged by the variations in cardiac size before and after treatment, it is obvious that the roentgenograms should be made during the same phase of the cardiac cycle.



A. *B.*

Fig. 5.—Cairokymograms. *A,* The kymographic exposure was initiated by the cardiocairograph during *diastole* (no delay device). Note that in each ventricular band the record starts in the maximum diastolic position of the ventricle, and, in the vascular bands, before ejection from the ventricles. *B,* The kymogram was initiated by the cardiocairograph during *systole* (with delay device). Note that in each ventricular band the record starts in the trough of the wave, or when systole is at its maximum, and, in the vascular bands, the record begins at the time of closure of the semilunar valves and the end of ejection.

Figs. 6*A* and 6*B* are cardiocairograms which were taken in quick succession, while respiration was suspended, but during opposite phases

of the cardiac cycle. There is a definite difference in the shape and size of the cardiac shadow.

Cardiocairography demonstrates the fallacy of the belief that a long exposure, lasting through several cardiac cycles, gives a shadow which represents the maximum diastolic size of the heart. The reasoning on which this conclusion was based is faulty, for the border of the heart in long exposures will naturally be the border bounding the unexposed region. This border is obviously that of the heart at the *moment of maximum systole.* Since, however, in long exposures there is no sharp border at all, an apparent border is visualized which lies somewhere between that of systole and that of diastole. Usually, this apparent border is quite different from the diastolic border. This is shown by Figs. 7*A* and 7*B*. Fig. 7*A* is a roentgenogram of the heart of a young adult, in diastole, taken with the cardiocairograph (1/30 second), and Fig. 7*B* is another of the same heart, taken immediately after, with a one-second exposure, during the same respiratory phase. The shadows differ both in shape and size; that obtained by the long exposure certainly does not represent the diastolic size of the heart.

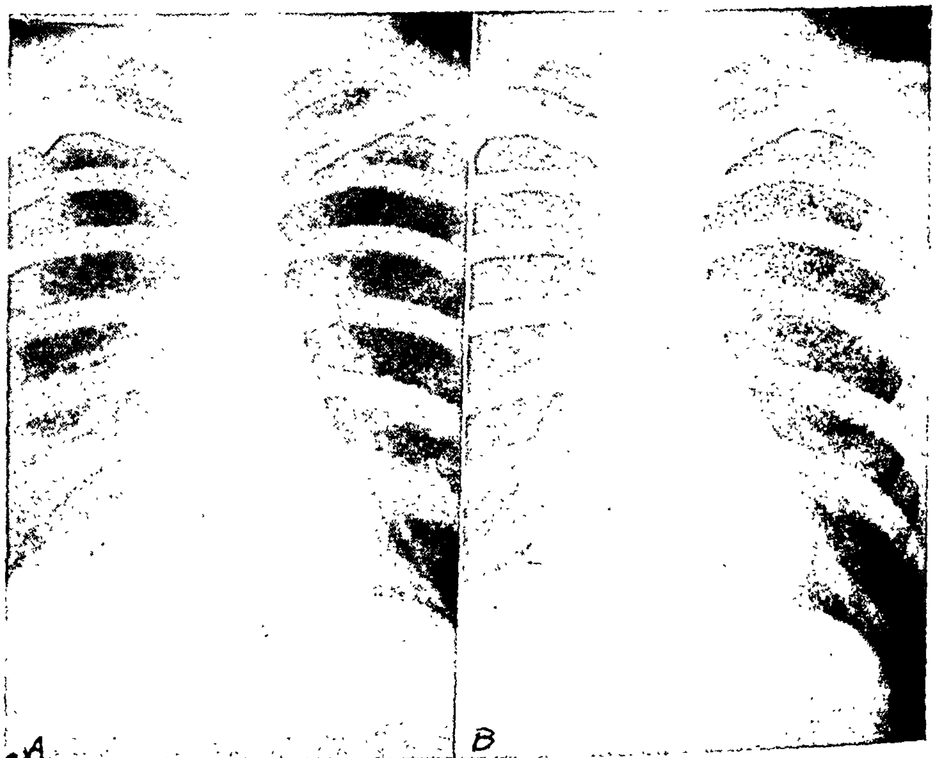


Fig. 6.—Cardiocairograms taken during opposite phases of cardiac action. *A*, Systole; *B*, diastole. The change in the cardiac contour is apparent.

For a comparison of cardiac contour, from time to time, in the same person, a standardized method for making the exposures always in diastole is obviously desirable. The one difficulty in obtaining perfect reduplication of the roentgenogram in every absolute and relative detail is that of maintaining the same respiratory phase during the ex-

posure. The error arising from this source may be minimized by immobilization of the diaphragm during very quiet respiration, preferably in inspiration.

2. The maximum degree of sharpness and detail of the pulmonic markings has been attained through the use of long focal distances, fine focal points, and rapid exposures. No further improvement is likely to be obtained, except through some method such as cardiocairography, whereby it becomes possible to make the exposure at the instant that the vascular structures are relatively at rest, namely, in ventricular diastole.

It has long been recognized that, in roentgenology of the chest, movement of the patient, or movement within his chest, is the most important single factor influencing definition and sharpness. The amount of blurring produced by movement varies with the rate of movement and with the duration of the exposure. If the movement of the patient cannot be controlled, the remedy is to shorten the exposure, but this does not take care of such movements as arise from the impact of the pulsating heart against the lungs and the pulsation of the vessels. The motion varies in relation to the cardiac cycle, and also in different portions of the lungs, depending upon the proximity of the vessels to the heart. Although at the periphery, in certain parts of the lung, the movement may be minimal, it may be as rapid as 20 mm. per second

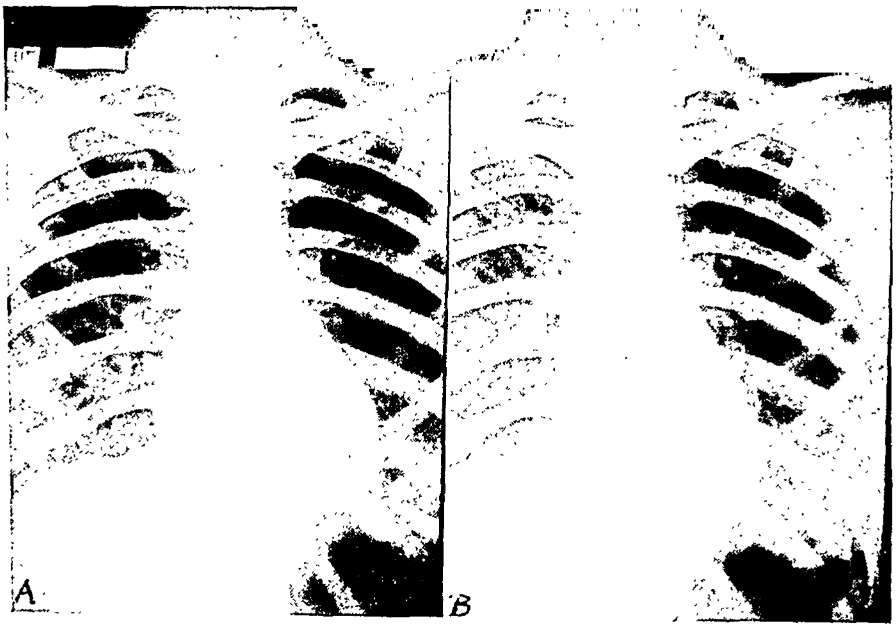


Fig. 7.—*A*, Cardiocairogram, during diastole. *B*, Simple roentgenogram of the same chest taken immediately afterward, with an exposure of one second. Note the difference in the size of the cardiac shadow. It is apparent that the long exposure does not show the shadow of the heart as it is in diastole. These records also demonstrate the improvement in definition and detail which comes with short exposure. All of the relative blurring with the long exposure is caused by vascular movement (Bouwers,[5] Wilsey[6]). The kilovoltage and distance for the two exposures were exactly the same. The time and milliamperage were naturally varied. That the subject did not move is evident from the sharpness of detail of ribs and diaphragm in both roentgenograms.

near the cardiac apex. In addition, the extent of the movement varies in different persons, and in the same person from time to time.

The movement of the pulmonary structures is at a minimum at that instant when the ventricles are almost at the end of the diastolic phase. This, therefore, is the ideal time for roentgen exposure of the lung. Such directed exposures, in contrast to fortuitous or undirected exposures, are therefore eminently desirable if we wish to obtain the maximum degree of sharpness of detail of the pulmonic structures.

It is only by means of a practical, technical device which makes the exposure when the effects of cardiac activity, as reflected in the movement of pulmonary structures, are at a minimum, that the maximum sharpness can be obtained. It cannot be fully attained by merely shortening the exposures. Thus, blurring of the cardiac margin and of other details may appear in exposures as short as 1/30, or even 1/60, second, if the exposure is made when the heart is in systole, and, with a normal pulse rate, almost half of the cycle is taken up with auricular and ventricular systole. The movement of the pulmonary markings and hilar shadows is caused by: (1) the pulse wave within the pulmonary arterial tree, which, traveling as it does at about 6 M. a second in the smaller vessels, straightens out the curves of elastic branching arteries, which are suspended in the elastic lung substance; (2) a slight and rapid vibration of the parenchyma in the neighborhood of the vessels; and (3) the actual vibration resulting from the impact of the heart against the lung.

This blurring, which is caused by the systolic discharge, is naturally most strikingly apparent in the shadows of structures adjacent to the heart. On the other hand, a longer exposure, of 1/10 or 1/20 second, if made during diastole, shows the arterial main stem shadow and its branches, crossed by a few venous and bronchial trunks, in sharp definition. The contrast between two exposures of the same chest, one made during systole and the other during diastole, demonstrates beyond doubt that the direct thrust of the heart on the lung and the displacement caused by changing pressures in the curved, elastic, large vessels play an important part in producing lack of sharpness. The distribution of branches in all directions tends to limit the displacement which occurs in many planes, depending upon the direction of curve of the individual branch. All this has a material effect upon detail.

The practical value of pulmonary cairography is that, because it gives sharpest recording of pulmonary markings, slight differences in general or local prominence are distinguishable, and early and slight infiltrative changes are discernible. Only by this method can a sharp, clear, and definite hilar shadow, with the details of the various structures which compose it, be obtained. The blurred hilar shadow caused by movement has been continually misinterpreted, for no other part of the pulmonic field is so easily affected by artifacts and extraneous shadows, and nowhere are sharpness and detail so important.

The cardiocairographic exposures refine stereoscopic roentgenography. In the ordinary stereoscopic examination the two exposures are fortuitously made. The individual roentgenograms show a definite difference in the size, shape, and direction of the markings and the hilar shadow. Of course, such roentgenograms fuse in the stereoscope, but there is no true accuracy in this fusing. In fact there cannot be, because the roentgenograms are made at different phases of the cardiac cycle. In actual practice it is unusual even for one roentgenogram of a stereoscopic pair to have been made during ventricular diastole. Usually, both show blurring, and, although this blurring is somewhat lessened by the stereoscope, the best stereoscopic results are not thus to be obtained; the blurring which is not diminished by the stereoscopic fusing may be regarded as indicating changes in the walls of the bronchi or interstitial tissue, when it is actually an artifact. Pairs of roentgenograms which are synchronized, however, and are made during the same phase of the cardiac cycle, particularly in late diastole, when the cardiac movement is at a minimum, give perfect fusion and astonishing clarity and richness of detail, not only in the pulmonary markings, but also in the hilar shadow, which shows clearly and legibly the rich detail of its complex structure.

McPhedran and Weyl,[4] Bouwers,[5] Bergk and Chantraine,[2] Wilsey,[6] Warren,[7] and McCoy[8] have discussed the degree of improvement in detail in the lung roentgenogram which is to be expected from synchronization of the exposure with cardiac diastole.

SUMMARY

Cardiocairography is a method by means of which roentgenographic examination of the heart can be made at a particular phase of its cycle. The apparatus designed by Schwarzschild for making such exposures of the thorax (the cardiocairograph) synchronizes the roentgen exposure with the action currents of the heart. These currents are taken through the standard leads of the electrocardiograph. Since the peak of the R wave is attained 0.08 second before the actual beginning of cardiac contraction, a roentgenographic exposure of the thorax at this instant will reveal the shape of the heart and the character of the lung fields during diastole.

Inasmuch as the time of occurrence of maximum systole is relatively constant, namely, about 0.20 second after the peak of the R wave, and is relatively independent of the pulse rate, and since the diastolic interval is that part of the cycle which varies most with the pulse rate, it becomes possible, by introducing into the circuit a delay mechanism, to obtain an exposure at the instant of maximum systole. Thus, roentgenograms of the chest may be obtained either when the heart is in maximum diastole or in systole.

The advantages and disadvantages of each type of exposure are discussed. The importance of establishing standards for the cardiac shadow, both during systole and diastole, is discussed.

In roentgenology of the chest, the motion of the pulmonary structures is the most important single factor influencing definition and sharpness of the images. The amount of blurring produced by movement varies with the rate of movement and with the duration of the exposure. Shortening of the exposure, even to $\frac{1}{30}$ second, does not eliminate movements which arise from the impact of the pulsating heart against the lungs and the pulsations of the vessels. This motion varies in relation to the cardiac cycle and in different portions of the lungs, depending upon the proximity of the vessels to the heart. Whereas at the periphery, in certain parts of the lung, the movement may be minimal, it may be very marked in the basal portions of the lungs. The movement of the pulmonary structures is at a minimum at the instant when the ventricles are almost at the end of the diastolic phase. This, therefore, is the ideal time for roentgen exposure of the lung. Further, in stereoscopic examinations of the chest, perfect visual fusion is obtained only if the two roentgen images of the lungs are made at exactly the same *phase of the cardiac cycle. This method gives a true stereoscopic pair* of roentgenograms which possess maximum sharpness and detail.

Cardiocairography may also be used to obtain kymograms in which the time scale begins at any predetermined phase of the cardiac cycle; this type of roentgenogram has been named the cairokymogram.

Further, cardiocairography provides a simple method for combined electrocardiographic and kymographic examination; it is free from many difficulties because there is no shielding problem in this procedure.

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THE EFFECT OF AMINOPHYLLIN ON PERIPHERAL BLOOD FLOW

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AMINOPHYLLIN (theophyllin-ethylenediamine) has been used clinically for the relief of cardiac pain, bronchial asthma,[1] acute pulmonary edema, paroxysmal dyspnea, Cheyne-Stokes respiration, intermittent claudication, and as a diuretic. It has been accepted by the Council on Pharmacy and Chemistry[2, 3] of the American Medical Association as a diuretic and cardiac stimulant; the Council was of the opinion that adequate data to indicate that it has an effect on coronary flow were lacking. There is certain evidence that it increases coronary flow in the experimental animal,[4, 5, 6, 7] but this has not been confirmed by all observers.[8] Many who have reported on its use for cardiac pain have attributed some effect to it,[9, 10, 11, 12] but others (Evans and Hoyle,[13] and Gold, Kwit, and Otto[14]), from a statistical analysis, were of the opinion that it had no specific beneficial effect on cardiac pain that could not be secured with a placebo. The opinion accepted by the Council is that the xanthines, as a group, exert no specific action on coronary blood flow which is useful in the relief of cardiac pain. On the other hand, Levy, et al.,[15] have recently reported observations which indicate that aminophyllin is effective in delaying the onset of angina of effort, presumably by increasing the coronary flow.

With respect to the effect of xanthines on peripheral vessels, Newell and Allen[16] found that fifteen patients with peripheral vascular disease showed an average rise of 1.8° C. in local skin temperature which lasted two hours after the administration of one of the xanthines (theobromine with sodium salicylate). Scuphan[17] obtained somewhat similar results with theobromine sodium acetate. More recently, however, McGovern, McDevitt, and Wright[18] have found that theobromine sodium salicylate, when given by mouth, was without benefit in the treatment of peripheral vascular disease. Thermocouples were used by these authors for the measurement of skin temperatures.

Starr, Gamble, Margolies, Donal, Joseph, and Eagle[19] gave aminophyllin (0.48 Gm.) intramuscularly to several patients and found that it had little or no effect on pulse and respiratory rates or on blood pressure, but that it greatly increased respiratory volume, cardiac output, and cardiac work. No electrocardiographic changes were observed. The basal metabolic rate was measured before, and from twenty to forty minutes following, the intramuscular injection of the drug; although there was, in most instances, a slight increase in metabolism,

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they did not consider it great enough to be of statistical significance. They concluded that aminophyllin was a powerful cardiac stimulant, but that its effect was underestimated because the estimate was usually based on changes in pulse rate, respiratory rate, and blood pressure.

Measurements and calculations of the thermal conductance of tissues were first made by Lefèvre, in 1911.[20] Burton,[21, 22] in 1934, used a "thermal circulation index" based on changes in internal and external body temperature and conductance of superficial tissues. Winslow, Herrington, and Gagge,[23, 24] in 1937, estimated the thermal conductance of superficial tissues, measured peripheral circulation from changes in conductance, and calculated the depth of the thermal gradient of the body. These studies have been continued and amplified by Hardy and Du Bois,[25] who used a calorimeter of their own construction. Hick, Keeton, Glickman, and Wall[26] have utilized these same principles for calculating an index to peripheral circulation in order to study changes caused by varying environmental conditions.

A method has recently been developed by Hardy and Soderstrom[27] for establishing an index of peripheral blood flow and estimating changes in peripheral blood flow. This method has been used by Du Bois, Hardy, and Soderstrom at the Russell Sage Institute of Pathology in conjunction with their calorimeter. We have modified their technique in such a way that average skin temperature, rectal temperature, and metabolic rate may be used to measure the effect of aminophyllin (theophyllin-ethylenediamine), when given intravenously, on the general peripheral circulation.

CALCULATIONS

When a subject is lying nude, in the basal state, with the environmental temperature below 28° C., it has been found that the skin is almost bloodless and is functioning like a dead insulator. As an insulator, the skin is known to be slightly more efficient than cork, which has a high thermal insulating quality.[20, 27] Hardy and Soderstrom[27] have found that the average conductance value for the nude and bloodless skin is in the neighborhood of 9.1 kilocals/C°/M²/hr. for men, and about 6.5 for women.

These values remain constant in environmental temperatures below 28° C. As blood flow to the skin increases, more heat is brought from the deeper tissues to the surface, so that the thermal conductance of the superficial tissues is increased. It is this change in thermal conductance that becomes an index to the peripheral circulation.

Hardy and Soderstrom[27] have devised the following formula for measuring peripheral blood flow:

$$F = 17S\left(\frac{Hl}{Tr - Ts} - \overset{\male}{9.1} \ \overset{\female}{(6.5)}\right) I$$

in which,

F = peripheral conductance above the minimal value
17 = factor for converting cal/C°/M²/hr. into c.c./min.
Hl = heat loss
Tr = mean rectal temperature
Ts = mean weighted skin temperature
9.1 = (kilocal/C°/M²/hr.) thermal conductivity of superficial tissue with minimum blood flow for males (6.5 for females)
S = surface area

F represents the heat which is carried to the surface by the blood stream in excess of the heat conducted by the tissues, and the value of F can be taken as a positive index of the volume of blood circulating near the skin surface. If the blood is assumed to start into the periphery at rectal temperature, and finally reaches the skin at skin temperature, F will represent this flow in cubic centimeters per minute, and, in this sense, F is a hypothetical quantity. This in no way detracts from its usefulness as a measure of the general vasomotor response.

In order to use this formula (I) in our observations, it was necessary to compute the heat loss (Hl) from the sum of the heat produced (Hp) and the heat storage (Hs), i.e., Hl = Hp + Hs (II). The heat produced (Hp) was ascertained by measuring the oxygen consumption, and the heat storage (Hs) was calculated from the following formula:

$$Hs = W \times 0.8\ (\triangle Tr \times 0.8 + \triangle Ts \times 0.2) \quad \text{III}$$

in which,

Hs = heat storage
W = body weight in kilograms
0.8 = average specific heat of body tissues
$\triangle Tr$ = change in rectal temperature
$\triangle Ts$ = change in skin temperature

In this equation ($\triangle Tr \times 0.8 + \triangle Ts \times 0.2$) represents the change in average body temperature. Hardy, Du Bois, and Soderstrom[28] have found by direct calorimetry that weighting the rectal temperature 80 per cent and the skin temperature 20 per cent gives the closest approximation of the average body temperature. Burton[29] used a different method and arrived at values of 65 and 35 per cent, respectively. Both agree that the use of surface temperatures leads to greater accuracy in calculating the average body temperature, and that the surface temperature is the more important, although the rectal temperature has the larger coefficient, on the average. Hardy, Du Bois, and Soderstrom[28] have pointed out that about 0.2 of the body mass is within 1 cm. of the skin surface. Weighting the skin temperature 20 per cent, therefore, is justified by evidence from several independent sources. The average temperature gradient of the body has been found by Hardy, Du Bois, and Soderstrom[28] to extend, on the average, 2.0 cm. below the surface. According to Winslow, Herrington, and Gagge,[23] the distance is 2.2 cm. In our studies, the values obtained by Hardy, Du Bois, and Soderstrom for weighting average body temperature and for the temperature gradient have been used.

After calculating the heat stored (III) and adding it to the heat produced (oxygen consumption), to obtain the heat lost (II), the result is substituted in the first equation, (I), in order to estimate the peripheral blood flow, that is to say, the blood flow in the peripheral tissues of the body to an average depth of 2.0 cm. below the surface, calculated in c.c. per minute. In persons with more than the average amount of subcutaneous fat, the normal, average, thermal conductivity of 9.1 for males is too high, and would indicate that the blood flow is less than zero; if the lowest result derived from $\frac{Hp + Hs}{Tr - Ts}$ is less than 9.1, its value, instead of 9.1, is used in the formula. If the result is less than zero when the female average thermal conductivity factor, 6.5, is used, the same procedure should be followed. It has already been stated that "F" represents the peripheral blood flow in cubic centimeters per minute. This value is divided by the body surface area in order to convert it to c.c./M^2/min.

In obtaining the average body-skin temperature, the radiometer readings, in degrees centigrade, from eleven points on the anterior surface of the body have been weighted according to the area of the body they represent, as described by Hardy, Du Bois, and Soderstrom[28] (Fig. 1).

METHODS

The "radiometer" described by Hardy[30] was used. With this apparatus it is possible to measure heat radiation from a uniform area of skin. Since, from the standpoint of radiation, the skin reacts as a "perfect black-body,"[31] *the radiometer is calibrated to read skin temperatures directly, in degrees centigrade. This is now* accepted as the most accurate method available for measuring skin temperatures.[32]

Subjects lying flat in bed perspire more in those parts of the body which are in contact with the mattress, and this causes a change in the skin temperatures in these regions. We were unable to circumvent this, as was done in observations carried out in the Russell Sage calorimeter, in which subjects lie on a bed made of fishing line, thereby eliminating this factor, as well as that of conduction. We recorded measurements of skin temperature from eleven places on the anterior surface, only, of the naked body; the body was covered with a sheet.

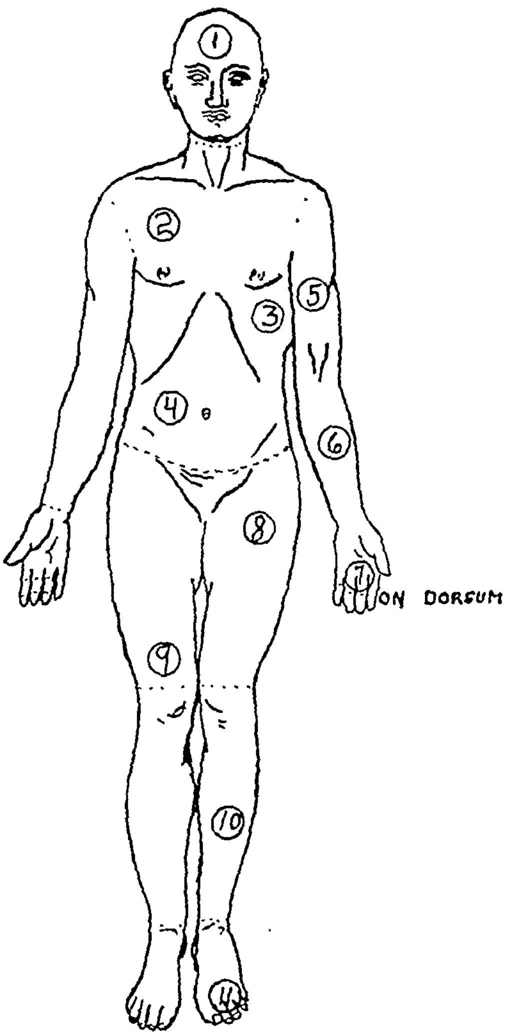

Fig. 1.—This figure shows the locations of individual areas over the body surface where skin temperatures were measured, and the division of the skin surface for weighting.

Average skin temperature $= (T_1 \times 0.07 + T_2 \times 0.14 + T_3 \times 0.05 + T_4 \times 0.07 + T_5 \times 0.13 + T_6 \times 0.19 + T_7 \times 0.35)$, in which,

T_1 = head temperature; 0.07 = weighting for head surface
T_2 = arm temperature; 0.14 = weighting for arm surface
T_3 = hand temperature; 0.05 = weighting for hand surface
T_4 = foot temperature; 0.07 = weighting for foot surface
T_5 = leg temperature; 0.13 = weighting for leg surface
T_6 = thigh temperature; 0.19 = weighting for thigh surface
T_7 = trunk temperature; 0.35 = weighting for trunk surface

The rectal thermometer consists of a single-junction thermocouple, as devised by Hardy and Soderstrom,[33] with the silver rectal junction inserted 5 to 10 cm. into the rectum, and the other junction immersed in water which is kept within two degrees of body temperature, in a pint thermos bottle. This thermometer is so connected that readings can be made from the galvanometer on the radiometer, which has been calibrated to give direct readings. The thermometer remained in place throughout the duration of each set of observations.

Oxygen consumption was measured with a Benedict-Roth metabolism apparatus. Surface area tables, utilizing the formula of Du Bois and Du Bois,[34] were employed in the calculations.

Observations were made in a room in which it was possible to maintain the temperature constantly within a range of one degree centigrade. The room was small, with only one window and one door. A metal screen was placed before the window, in order to keep heat loss from convection to a minimum. By persistent attention to door and window, it was possible to keep the variation in room temperature down to one degree centigrade. Since Du Bois[35] and Hardy and Soderstrom[27] have shown that, in environmental temperatures below 28° C., the conductance value of the skin of nude subjects does not change, and that vaporization below 30° C. also changes very little, we maintained the temperature of the room in which our studies were made below 27° C. during our observations, in order to keep these factors as nearly constant as possible. Inasmuch as most of the observations were carried out during the winter months, and the room was heated by a steam radiator, the room humidity, although not measured, was necessarily low.

Blood pressures were measured with a mercury sphygmomanometer.

The patients were accustomed to hospital routine, but had not been trained for these procedures. Emotion may have a marked effect upon the circulation in the hands, causing large and rapid changes in skin temperature (Wolff and Mittelmann[36]). The effect of emotion on the average skin temperature is, however, not known. It is possible that changes in the temperature of the hands caused by emotion may be compensated for by changes in skin temperatures elsewhere in the body.

Emotional factors were eliminated as far as possible by maintaining a pleasant rapport with the patients, by explaining the procedure to those who were interested, and by reassurance. For the most part, they cooperated well. A few patients began to show signs of restlessness and irritability after lying supine for two or more hours. The data were discarded when the subject refused to cooperate.

The calculation of heat loss by the method we have employed does not vitiate the significance of these observations, for Burton, and Winslow, Herrington and Gagge, and Du Bois have used this calculation and compared it with actual measurements of heat loss obtained by direct calorimetry, and have found that it gives results sufficiently accurate for our purpose.

A few observations were made by us to ascertain the effect on the skin temperatures and peripheral blood flow of taking alcohol and warm water internally; the changes which we observed were comparable to those found in similar studies which had been carried out in the calorimeter by Du Bois and Hardy. In short, both alcohol (25 to 50 c.c. of 95 per cent) and warm water (900 c.c. at 53° C.), when given by mouth, produce an increase in peripheral blood flow. That the methods which we utilized yielded results similar to those of Du Bois and Hardy, who employed the calorimeter, gave us confidence that they were suitable for the purpose for which we wished to use them.

Studies were made of patients from the pavilions of the hospital. Patients numbered I to XI, inclusive, had no evidence of cardiac disease. In these cases the diagnoses were sciatica (I), gonorrheal arthritis (II), gastric ulcer (III), chronic glomerulonephritis (IV), acute glomerulonephritis (V), hyperthyroidism (VI), thromboangiitis obliterans (VII), diverticulitis (VIII), multiple sclerosis (IX), gastrointestinal hemorrhage, with neurosis (X), and (postoperative) gumma of the

testicle (syphilis) (XI). In the cases in which there were manifestations of cardiac disease (XII to XX inclusive), the diagnoses were vena caval obstruction (XII), rheumatic heart disease (XIII), chronic constrictive pericarditis (XIV), rheumatic heart disease (XV), acute rheumatic carditis (XVI), cardiovascular-renal disease (XVII), chronic constrictive pericarditis (XVIII), old coronary occlusion (XIX), and aneurysm of the aorta (XX). The observations which were made on each patient are shown in Table I. Studies which were made when cardiac patients had congestive heart failure are indicated by "decompensated" after the number of the patient. Those cardiac patients (XII through XX) without this qualification had no congestive failure.

PLAN OF OBSERVATIONS

Observations were made before and after the injection of aminophyllin* intravenously. When the study was first inaugurated, 0.24 Gm. of the drug was given, but when it was found that this amount was usually without effect, we increased the dose to 0.48 Gm. In order to be certain that the effects which we observed were not to be attributed to venepuncture and injecting fluid, per se, in several cases we observed the effect on blood flow of injecting 20 c.c. of physiologic salt solution. The procedure was identical, except that saline was injected instead of aminophyllin. Those subjects whose peripheral blood flow was unaffected by the smaller amount of aminophyllin (0.24 Gm.) also served as controls.

All observations were made with the patients in a basal metabolic state. Each subject lay quietly in bed, naked, covered with a sheet, for an hour, in order to allow for adjustment of the peripheral circulation to environmental conditions. The oxygen consumption was then measured, after which the first series of skin temperatures, the room temperature, the rectal temperature, and the blood pressure were recorded in sequence. Three sets of readings were made at intervals of fifteen to twenty minutes, from which it was possible to calculate peripheral blood flow for two preliminary periods; this served as a base line. Immediately after the third series of readings, the patient was given an intravenous injection, after which another series of readings of temperatures was recorded as rapidly as possible, followed by measurement of the oxygen consumption. Data were collected at intervals of fifteen to thirty minutes during the next one to two hours, in order to observe the duration of the action of the drug.

The results of thirty-four observations on twenty patients were analyzed (Table I). In five instances, 20 c.c. of physiologic saline were injected intravenously; in four, 0.24 Gm. of aminophyllin, and, in the remaining 25, 0.48 Gm. of aminophyllin.

RESULTS

The effect of 0.48 Gm. of aminophyllin was recorded in twenty-five instances (Table I). In twenty of these, the peripheral blood flow during the second 15-minute preliminary period before the injection was either the same, or less, than it was during the first 15-minute period. In the other 5, a slight increase occurred during the second preinjection period. From our data it appears that changes of less than 35 c.c./M²/min. are not significant. This criterion has been used in analyzing our results.

On eighteen occasions, there was an immediate increase in peripheral blood flow (Table I) (Fig. 2), amounting to 40 to 195 c.c./M²/min., after the injection of 0.48 Gm. of aminophyllin. On four occasions,

*We wish to thank the H. E. Dubin Laboratories for supplying us with the aminophyllin used in these studies.

little or no effect was observed (Fig. 3), and, on three others (Table I), there was an immediate decrease, or no significant change, in peripheral blood flow, followed, in the next period, by an increase above the control level amounting to from 52 to 83 c.c./M²/min. (Fig. 4). We have called this a "delayed" response. In seventeen instances, an increase in peripheral flow was followed by decrease in the next period. In certain cases the decrease was gradual; in others, there was a precipitous fall to, or below, the preinjection level of blood flow. In four instances, however, the increase in blood flow persisted for thirty minutes. The individual variations in response are shown in a frequency diagram (Fig. 5).

No significant change in peripheral blood flow occurred in the five instances in which physiologic saline was injected (Table I) (Fig. 6). In three cases, in which 0.24 Gm. of aminophyllin was injected slowly,

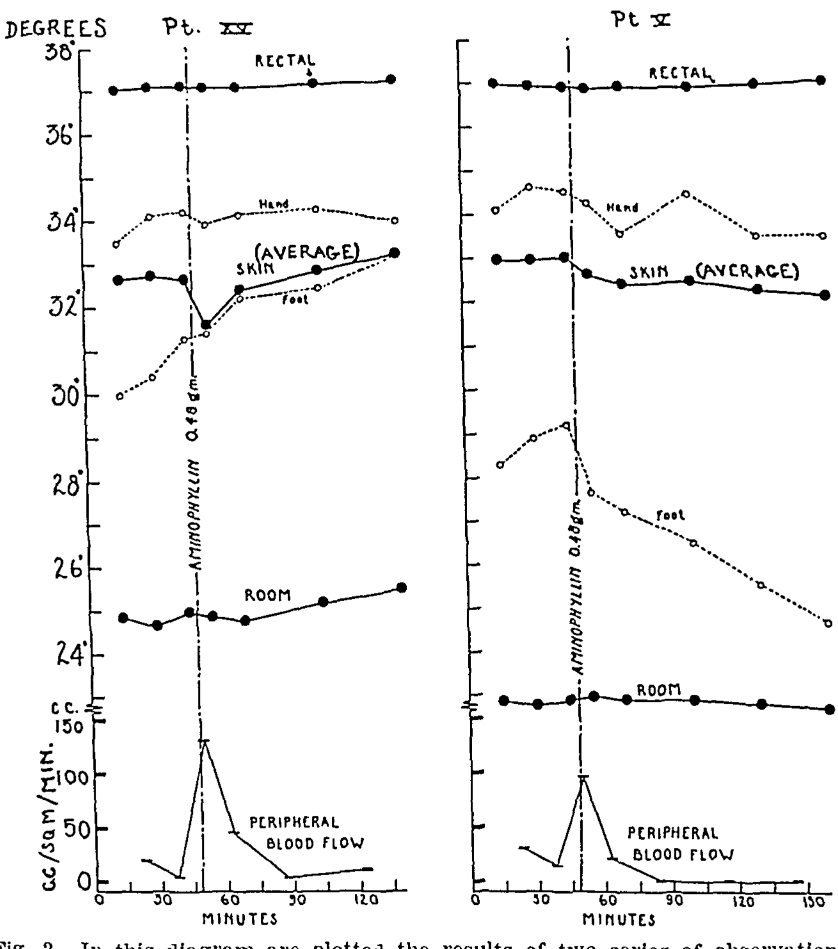

Fig. 2.—In this diagram are plotted the results of two series of observations (patients XV and V, respectively), illustrating the most frequent response of the peripheral blood flow to the intravenous injection of 0.48 Gm. aminophyllin, namely, an increase. The peripheral blood flow has been calculated in c.c./M²/min. for each period between consecutive observations of skin and rectal temperatures, and is plotted as a short horizontal line representing the average peripheral blood flow for each period. In this and the following similar diagrams, showing the effect of aminophyllin, the following observations are emphasized: the very slight changes in rectal temperature, the greater variability of average skin temperature and the fall in average skin temperature when an increase in peripheral blood flow occurs, and marked variability in the temperatures of the hands and feet.

TABLE I

SUMMARY OF THIRTY-FOUR OBSERVATIONS RELATING TO THE PERIPHERAL BLOOD FLOW OF TWENTY PATIENTS

INTRAVENOUS INJECTION	EFFECT ON PERIPHERAL BLOOD FLOW—NUMBER OF OBSERVATIONS				TOTAL NUMBER
	NO CHANGE*	INCREASE†		DECREASE	
		IMMEDIATE	DELAYED		
Physiologic salt solution 20 c.c.	5 (XI,‡ XVI, XVII, XIX, XX)	0	0	0	5
0.24 Gm. aminophyllin	3 (I, II, XVI)	1 (X)	0	0	4
0.48 Gm. aminophyllin	4 (VIII, VIII, IX, XVIII decompensated)	18 (I, II, III, IV, IV, V, V, VI, VII, XII decompensated, XII decompensated, XII compensated, XIII, XIV, XV decompensated, XV compensated, XVI, XVII)	3 (XIII, XIV, XVIII decompensated)	0	25

*The change in peripheral blood flow was less than 35 c.c./M²/min.
†The change in peripheral blood flow was greater than 35 c.c./M²/min.
‡See pp. 209 and 210 for diagnoses in the cases to which the Roman numerals refer.

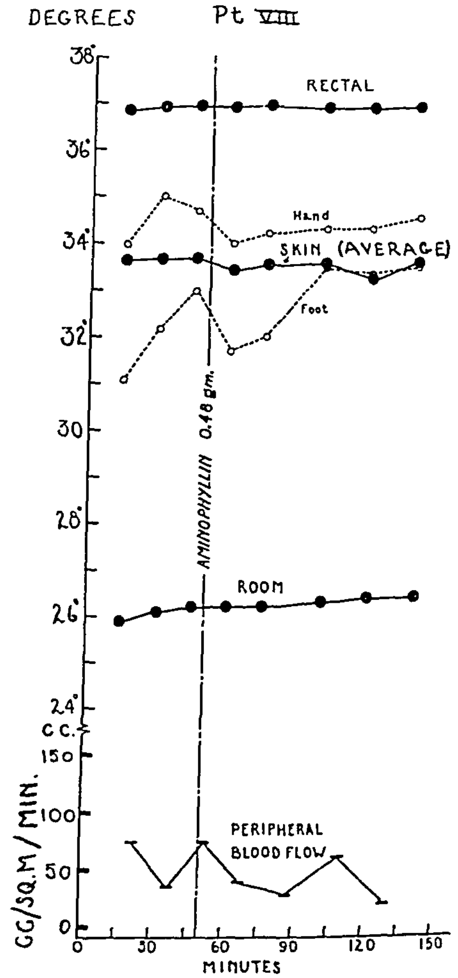

Fig. 3.—In this diagram are plotted the data from one case (VIII) in which there was no significant change in peripheral blood flow when 0.48 Gm. of aminophyllin was injected intravenously. A slight increase occurred, but it was less than 35 c.c./M²/min., which was arbitrarily chosen as the minimum significant increase in peripheral blood flow.

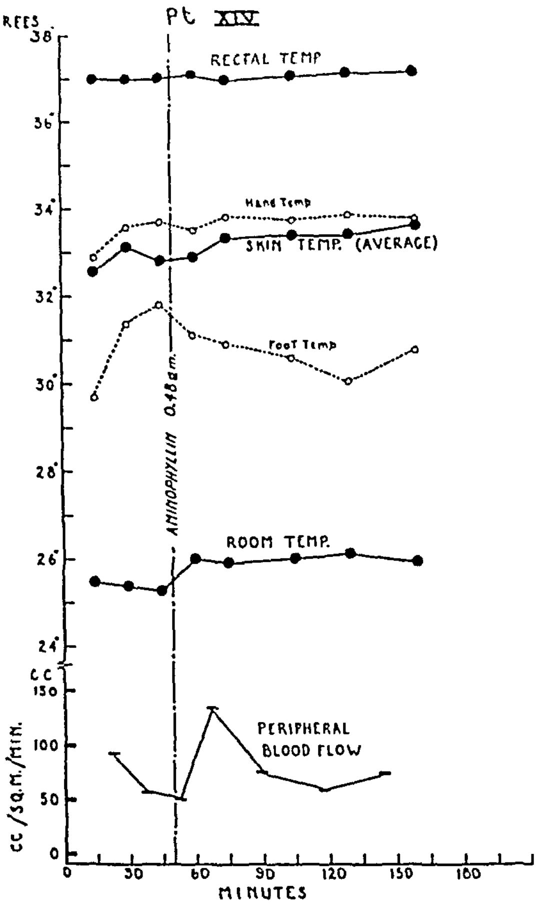

Fig. 4.—In this diagram are plotted the data from one representative series of observations (XIV) in which the response to 0.48 Gm. of aminophyllin was delayed.

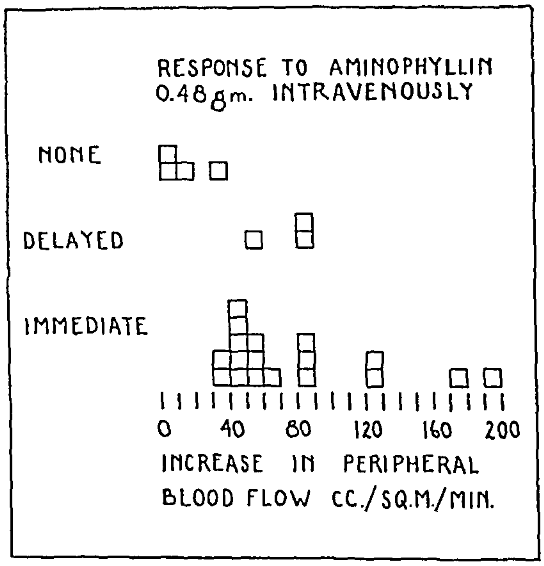

Fig. 5.—In this figure are plotted, in a frequency diagram, the responses of the peripheral circulation to the intravenous injection of aminophyllin, in doses of 0.48 Gm., on twenty-five occasions. The observations are divided according to whether the response was immediate, delayed, or "none," and according to the amount of increase in peripheral blood flow. The marked variability in the response of individual patients is shown. The apparent overlapping in the 30-40 c.c./M²/min. increase in peripheral circulation range in this diagram is the result of having chosen an increase of 35 c.c./M²/min. as the minimum significant response.

there was no significant effect on peripheral blood flow; in one (X), however, there was a rise of 102 c.c./M²/min., which compares favorably with that which occurred when the larger amount was given (Table I). This patient suffered from a severe anxiety neurosis, and was greatly frightened by the venepuncture; since this was the only instance in which the skin temperature rose after the injection of 0.24 Gm. of the drug, we were of the opinion that the increase in peripheral blood flow was of psychic origin. Those patients who received the smaller dose of aminophyllin, which produced no changes in the circulation (I, II, XVI), supplement the controls who were given physiologic saline.

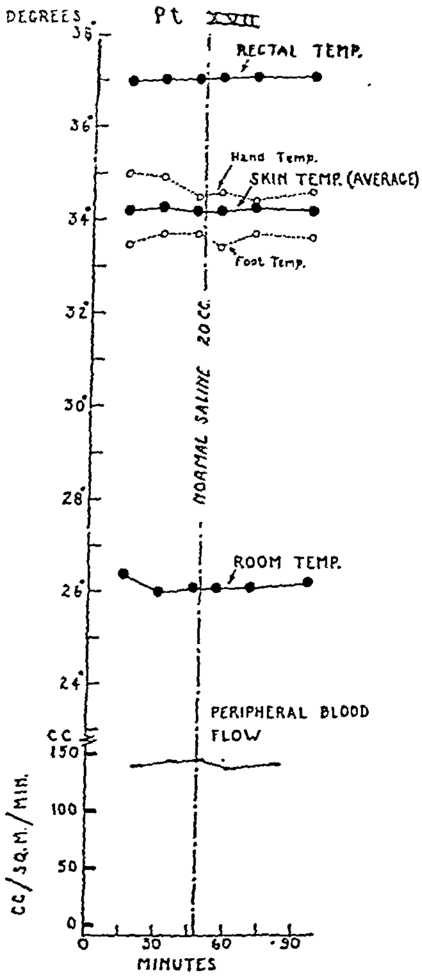

Fig. 6.—In this diagram are plotted the data in Case XVII, in which physiologic saline was given intravenously instead of aminophyllin. No significant change in peripheral blood flow occurred.

The basal metabolic rate twenty, or more, minutes after the injection of the drug was about the same as before the injection, except in two cases, in which a marked rise in heat production occurred. It was not possible to measure the oxygen consumption sooner, because of the desirability of recording the skin temperatures first. If aminophyllin exerted a transient effect on oxygen consumption, it was not detected in these studies. In order to secure data on this point, the basal metabolic

rates of five patients were measured before, and immediately after, the intravenous injection of 0.48 Gm. of aminophyllin. In two instances, no change in basal metabolic rate occurred, in one, it increased 4 per cent, and, in two, it rose 9 per cent immediately after the drug was injected. In short, the change in blood flow which we have observed is not to be attributed to a rise in basal metabolic rate.

In eight cases (IV, V, VIII, XII, XIII, XIV, XV, XVIII), the effect of aminophyllin on blood flow was studied a second time (Table I); in seven of these, the response was the same on both occasions, namely, an increase. In the case of one patient (XVIII), vasodilatation resulted on one occasion, and vasoconstriction on the other. No explanation could be found for these differing responses in this last case.

Because of obvious technical difficulties, it was not possible for us to measure peripheral blood flow and cardiac output simultaneously. In one case, however, the cardiac output was measured by the Grollman technique[37, 38] before and after the injection of 0.48 Gm. of aminophyllin intravenously. The cardiac output, which had been 3.63 L./min. immediately before the drug was given, increased to 4.68 L./min. five minutes after injection, a rise of 30 per cent (Table II), without change in pulse rate. On the day preceding the measurements of cardiac output, as well as on the following day, injection of the drug resulted in an increase in peripheral blood flow of 50 c.c./M^2/min.

DISCUSSION

Analysis of the preliminary periods, before aminophyllin was given, showed that, at the prevailing temperature, the peripheral circulatory mechanism was still adjusting itself to the constant environmental temperature. An environmental temperature below 28° C. should cause the peripheral circulation to decrease to a minimum. This did not occur in these studies, for at all times the subjects were covered by a sheet, and skin temperature measurements were made under the sheet. To attain the minimum peripheral blood flow, it was necessary to provide an environmental temperature somewhat lower than 28° C. The environmental temperature was kept constant within a range of one degree centigrade during the duration of each experiment, and always below 27° C., but the range for the observations on different days was 23° C. to 27° C. Since we were unable to duplicate environmental conditions exactly, from day to day, correlations could not be made between environmental temperature and basal peripheral blood flow.

When a sufficient amount of aminophyllin (0.48 Gm.) was given intravenously, an increase in peripheral blood flow occurred in most instances (Table I) (Fig. 2). The effect was of short duration, except on four occasions. The magnitude of the increase in peripheral flow showed large variations from patient to patient (Fig. 5). In four instances (VIII, VIII, IX, XVIII, decompensated) (Table I), no changes were observed (Fig. 3), and, in three others (XIII, XIV, XVIII, de-

TABLE II

THE EFFECT OF AMINOPHYLLIN ON THE CARDIAC OUTPUT OF PATIENT XII, MALE, AGED 68 YEARS ON FEB. 11, 1939

TIME	BODY SURFACE	OXYGEN CONSUMPTION	BASAL METABOLIC RATE	ARTERIO-VENOUS OXYGEN DIFFERENCE	CARDIAC OUTPUT	CARDIAC OUTPUT	CARDIAC RATE	CARDIAC OUTPUT PER BEAT	BLOOD PRESSURE	LEFT VENTRICULAR WORK	CHANGE IN CARDIAC OUTPUT
	sq.m.	c.c./min.	per cent	c.c.	L./min.	L./sq.m./min.	per min.	c.c.	mm.Hg.	gm.m. per beat	per cent
10:21 A.M.	1.97	292	+21	80.6	3.63	1.84	68	53	120/70	68.5	
10:53 A.M.				. . . . aminophyllin 0.48 Gm. intravenously							
10:58 A.M.	1.97	294	+22	62.8	4.68	2.37	68	69		89.2	+30

compensated) (Table I), an initial decrease in peripheral flow occurred, followed by an increase (Fig. 4). Such variations in type and degree of response are to be expected in any study of the effects of a drug on such a complex organism as man. These studies show that aminophyllin, when given rapidly, in doses of 0.48 Gm., intravenously, usually causes an increase in peripheral blood flow.

These twenty-five experiments were analyzed with respect to whether or not the patient suffered from cardiac disease. Eight experiments (XII, XIII, XIII, XIV, XIV, XV, XVI, XVII) were done on six cardiac patients who did not have congestive heart failure (Table I), and five experiments (VIII, VIII, XII, XII, XV) on three patients who had congestive heart failure (Table I). Twelve sets of observations (I, II, III, IV, IV, V, V, VI, VII, VIII, VIII, IX) were made on nine patients who showed no evidence of cardiac disease (Table I). From an analysis of the frequency diagram (Fig. 7), it is apparent that responses to aminophyllin vary from patient to patient, and that the peripheral circulatory response to aminophyllin is not dependent upon the presence or absence of cardiac disease. Moreover, there was no difference in its effect when heart failure was present and after recovery from heart failure in the two cases in which it was possible to make this comparison (XII, XV) (Table I).

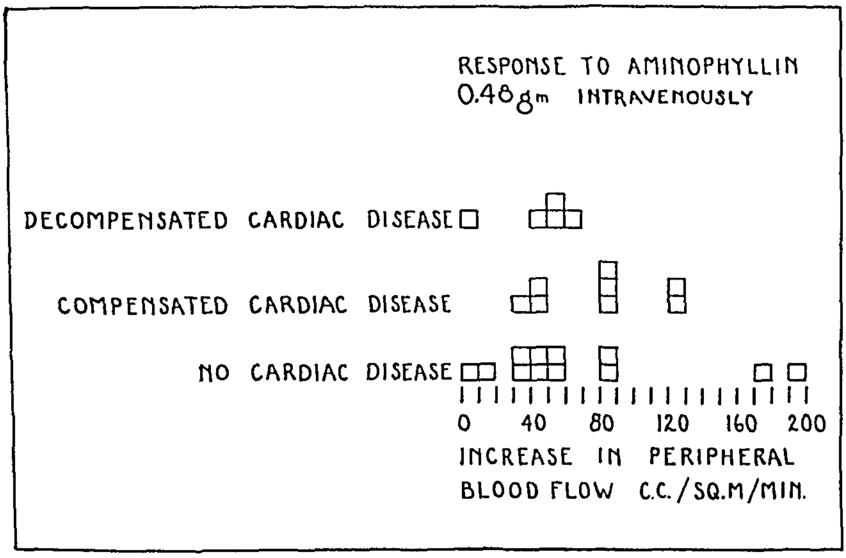

Fig. 7.—In this figure the data in Fig. 5 are plotted, as a frequency diagram, to show the effect of the functional state of the heart on the response of the peripheral circulation to 0.48 Gm. of aminophyllin. No correlation is apparent.

Measurements of cardiac output before and after aminophyllin was given showed that the drug increased the cardiac output to a degree sufficient to provide for the amount required by the increase in peripheral blood flow in the same patient. In short, since aminophyllin increases the cardiac output, there is sufficient blood to provide for the increase in peripheral flow, without redistribution of the circulating blood volume.

The effect of rate of injection of the drug was observed. When injected at the rate recommended by the manufacturers (five minutes for each 5 c.c. of solution, containing 0.24 Gm. of the drug), no unpleasant reactions, except an occasional feeling of warmth or tingling about the face, were observed. When the drug was given rapidly, however, the patients experienced several unpleasant reactions. These were sensations of warmth over the body, especially about the face and neck, slight to moderate generalized perspiration, tingling of the hands, blue vision, a rise in blood pressure, nausea, and, in one instance, a sense of constriction in the chest. These symptoms have been described by Herrmann, Aynesworth, and Martin.[1] In none of our patients did vomiting, twitching, convulsions, or coma occur. Two of our patients complained of headache which lasted throughout the rest of the day.

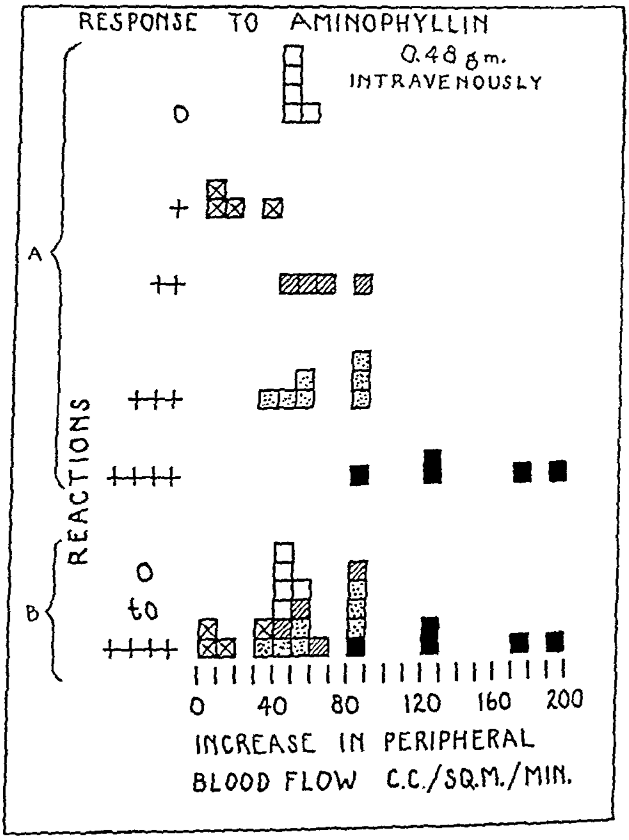

Fig. 8.—In this figure are plotted, as a frequency diagram, the increase in the peripheral blood flow following the injection of 0.48 Gm. of aminophyllin, against the reaction experienced by the patient while the drug was being given. 0 = no symptoms; + = tingling in hands and face; ++ = tingling, lightheadedness and slight sweating; +++ = tingling, lightheadedness, moderate sweating, and increase in blood pressure; ++++ = tingling, lightheadedness, sweating, increase in blood pressure, and nausea. In *A*, the reactions are separated, and, in *B*, they are plotted in the same diagram, with the symbols the same as in *A*. It appears that the more severe the reaction, the greater the increase in peripheral blood flow.

The rate of injection and the subjective and objective symptoms caused by rapid injection are mentioned because the production of diaphoresis was one of the most constant effects of the drug, and appeared to be more marked the more rapidly the drug was injected. Moreover, the

more severe the reaction, the greater the increase in peripheral blood flow (Fig. 8). Likewise, when there was an increase in peripheral blood flow after the injection of aminophyllin, it was accompanied in all except one case by a fall in average skin temperature. This was, without doubt, caused by the increased sweating. There was no significant change in rectal temperature, however. The patients whose perspiration was detected by the examiner showed an average increase in peripheral blood flow of 89 c.c./M^2/min., whereas those whose perspiration could not be seen or felt showed an average increase of 36 c.c./M^2/min. Importance is attached to this observation because increased circulation to the skin indicates increased heat loss from the skin, and this increased heat loss from the skin was accompanied by a fall in average skin temperature. This observation substantiates a concept formulated by Barr and Du Bois[39] over twenty years ago, one to which Du Bois has called attention since,[35, 40] namely, that it is possible for the body to lose more heat through a cool skin than through a warm one.

It is known that the skin temperatures of the hands and feet are much more labile than those of the rest of the body. Both the palms and the soles were avoided because of the tendency for perspiration to occur in these regions. The measurements were taken, therefore, over the dorsum of the fingers and over the flexor surfaces of the feet at the metatarsophalangeal joints.

The skin temperatures of the hands were higher than the average body temperatures in twenty-three of the twenty-five experiments, and the changes in skin temperature of the hands roughly followed those in average body skin temperature, although the changes in the former were much more marked. Most of the hand temperatures lay between the average skin and rectal temperatures. When aminophyllin was given, the skin temperature of the hands fell, as did the average skin temperature of the whole body.

The skin temperatures of the feet were far less constant than those of the hands. They were far below the average skin temperatures, with the exception of one patient who was suffering from chronic constrictive pericarditis and had signs of congestive heart failure. In this case, the temperatures of the feet were higher than the hand temperatures. Moreover, the skin temperatures of the feet were more responsive to room temperature. If this was below 25° C., the temperature of the feet fell throughout the duration of the experiment, but, if it was above 25° C., the feet temperatures were more likely to rise during the period of study. There appeared to be no correlation between skin temperatures of the feet and of the other areas.

The surface temperature of the hands and feet may fluctuate widely as a result of emotion, changes in environmental temperature, and increased perspiration, although the average body temperature during

the same interval may change only slightly. This is shown in the diagrams (Figs. 2, 3, 4, and 5) in which hand and foot temperatures have been plotted. The temperatures of the hands and feet do not serve as an index of the average surface temperature of the entire body.

In two instances there was a marked increase in basal metabolic rate after aminophyllin had been given, but in one the rise appeared to be the result of lack of cooperation on the part of the patient, and in the other it was attributed to a cardiac irregularity. If these two cases are discarded, the average change in basal metabolic rate was 2.8 cal./hr.; there were as many increases as decreases. Supplementary observations on the metabolic rate immediately after the administration of aminophyllin likewise showed no significant change. The severity of reaction to the drug did not appear to affect the basal metabolic rate. Half of the patients who had a severe reaction showed a slight rise in oxygen consumption, and the other half a slight fall. It appears, as Starr, Gamble, Margolies, Donal, Joseph, and Eagle[19] have maintained, that the drug does not have a significant effect on basal metabolic rate.

CONCLUSIONS

1. The average skin temperature was utilized for measuring the peripheral blood flow and changes in peripheral blood flow resulting from the intravenous injection of aminophyllin.

2. In twenty-one of twenty-five cases, 0.48 Gm. of aminophyllin, when given intravenously, produced an increase in peripheral blood flow which persisted only a few minutes.

3. Rapid injection of the drug increased this effect.

4. The increase in peripheral blood flow was accompanied by a fall in skin temperature caused by sweating, and, as the skin became cooler, the body lost more heat.

5. The skin temperatures of the hands and feet vary much more than those of other parts of the body, but do not appear to have a significant effect upon average body temperature. The skin temperature of the extremities is not an index of the average skin temperature of the whole body.

6. Aminophyllin produces no significant changes in oxygen consumption.

7. Aminophyllin, when given in doses of 0.48 Gm., intravenously, increases the cardiac output. The increased amount of blood is available for the augmented circulation in the skin, without redistribution of the circulatory blood volume.

We are very much indebted to Dr. James Hardy, who has freely given his help and guidance in the use of the method, criticism of the data, and in preparation of the manuscript.

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DISSECTING ANEURYSM

A Report of Nineteen Cases, With a Review of the Recent American Literature

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IN AN extensive review of the world literature, published in 1933, Shennan[1] was able to collect 300 cases of dissecting aneurysm of the aorta, to which he added seventeen of his own. In only six of these cases had an ante-mortem diagnosis been made. From that date until Jan. 1, 1939, eighty-two additional cases[2-32] have been reported in the American literature, in twenty-six of which the correct diagnosis was made. To this number we are adding nineteen authentic cases of dissecting aneurysm of the aorta, taken from the records of Charity Hospital of Louisiana at New Orleans, in two of which the diagnosis was made ante mortem.

McGeachy and Paullin[2] have given an excellent, brief account of the history of our knowledge of aortic aneurysm, from which we quote:

"Nicholls, in 1728, demonstrated that rupture of the inner coat of the aorta could occur in the absence of rupture of the outer coat, and, in 1761, described a dissecting aneurysm found at autopsy on King George II of England. Morgagni reported a case in 1769, and, in 1798, Lynn added to the literature a most interesting account of a dissecting aneurysm in which rupture had occurred during labor. Laënnec, in 1819, was the first to use the term 'dissecting aneurysm.' The first American case was reported by Pennock,[33] in 1838. Swain[34] is credited with the first correct ante-mortem diagnosis, in 1856, and, in 1863, Peacock[35] published a complete description of the clinical and pathologic picture, based on an analysis of eighty collected cases."

INCIDENCE

McGeachy and Paullin[2] state that the incidence of dissecting aneurysm of the aorta is 1 in every 500 necropsies; Weiss[24] places it at 1 in every 200, and Farinacci,[3] at 1 in every 224; Glendy, Castleman, and White[7] say that it is 1 in every 430, and Perry[5] estimates that it is 1 in every 552. The average of these ratios amounts to 1 in every 381 necropsies.[5] Harris[17] estimates that approximately 85 per cent of all incomplete, spontaneous ruptures of the aorta terminate as complete perforations, and approximately 15 per cent as dissecting aneurysms.

The literature shows that men are affected twice as frequently as women, and that the highest incidence occurs in the fourth, fifth, and

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sixth decades of life. On the other hand, Klatz and Simpson[36] were able to collect forty-two cases of dissecting aneurysm in persons under 40 years of age, two of whom were juvenile, and seven adolescent. In Shennan's[1] collection, the women outnumbered the men in the eighth and ninth decades.

THEORIES OF ETIOLOGY

A number of theories have been advanced to explain the origin of dissecting aneurysm. The mechanical theory postulates a sudden cardiovascular strain in a person with a normal, or apparently normal, cardiovascular system, but Klatz and Simpson's[36] work makes this hypothesis doubtful. They subjected normal aortas, in fresh cadavers, to intraluminal pressures of 1,000 mm. Hg, without causing rupture, and they cite other similar experiments,[37, 39] in which the intraluminal pressure was raised to 3,000 mm. Hg, without ill effects.

Some authors believe that the aortic wall must be diseased before rupture can occur, regardless of whether or not cardiovascular strain is a precipitating factor. The idea[7, 24] that disease of the intima is the important etiological factor in dissecting aneurysm appears to be losing ground, as reports accumulate of young subjects in whom no intimal disease is demonstrable. Also against the theory is the observation[2, 24, 36] *that dissecting aneurysms which begin at the site of ulcers or atheromatous plaques are usually restricted in extent.*

Other theories[7, 40] presuppose the existence of an abnormal tunica media. Degenerative changes in the media, secondary to obliterative arteriosclerosis of the vasa vasorum, were first described by Tyson,[41] and the cases reported by Kellogg and Heald[42] and by Whitman and Stein[43] seem to emphasize the importance of this mechanism.

Moritz[44] credits Erdheim with the recognition of essential medial damage of local or diffuse character which is not secondary to obliterative disease of the vasa vasorum. The degeneration, Moritz continues, is a chromatrophic or mucinous process, probably involutional or senescent in character, which is most intense at the site of the primary rupture; microscopic study may be required to demonstrate it. It may progress to cyst formation or to vacuolation.

Congenital deformities of the aorta,[4, 6, 24, 33-35, 45, 46] such as coarctation and hypoplasia, are undoubtedly the etiologic factors in certain cases of dissecting aneurysm. It has been estimated[6] that about 16 per cent of patients with coarctation of the aorta eventually develop this condition.

The apparent lack of connection between syphilitic mesaortitis and dissecting aneurysm is interesting. Weiss[24] even regards the presence of syphilitic aortitis as evidence against the possibility of dissecting aneurysm and states that the occasional joint occurrence of the two conditions is merely coincidental. He reported a case in which the dissecting aneurysm arose at a point removed from a saccular syphilitic

aneurysm, and dissected around it. Others[36] confirm his idea that syphilitic aortitis seals the elastic laminae together and makes dissection difficult, if not entirely impossible.

PATHOLOGY

The gross pathologic changes in dissecting aneurysm are readily followed. A primary rent, ordinarily varying in length from 0.25 to several centimeters, occurs in the aortic intima. The intima is usually normal at the site of the tear. Ordinarily, the long axis of the tear is collinear with that of the arterial lumen. The most frequent sites are, in the order listed, the ascending aorta, from 0.5 to 3 cm. above the aortic valves, the junction of the ascending and transverse portions, and the junction of the transverse and descending portions. Longitudinal tears are most common in the ascending portions of the aorta,[1, 2, 45, 47] and transverse and longitudinal tears are about equal in incidence on the greater curvature of the arch.[1]

After the tear has occurred, the dissecting column of blood usually penetrates the aortic wall radially from the site of the rupture to a point in the media at the junction of its outer and middle thirds. From this point a cleavage plane is created between the elastic laminae, involving from one-half to three-quarters of the circumference of the vessel adjacent to the tear. Dissection usually continues in the direction of the intraluminal blood flow, but may be directed simultaneously toward the heart, particularly in those cases in which the primary intimal tear is located in the ascending or transverse segments of the aortic arch. Osgood and his associates[28] estimated that 10 per cent of the ruptures in these locations are attended with dissection toward the heart.

The dissection may involve the entire length of the aorta and may extend throughout the iliac arteries or almost any other branch of the aorta. It has been estimated[1, 2, 7, 9] that dissection is limited to the ascending and transverse portions of the aorta in 30 per cent of all cases, and extends to the abdominal aorta in 35 per cent.[28]

After the dissecting column of blood has gained access to an intramedial cleavage plane, a secondary rupture outward may occur at any point along the aortic wall. The most frequent result of secondary rupture is hemorrhage into the mediastinum. Hemorrhage into the pericardial, pleural, or abdominal cavity is less common. Hemorrhage into the pleural cavity occurs more often on the left than on the right side.[2, 24] Secondary rupture into the aortic lumen occurs in from 10 to 15 per cent of all cases.[47, 48] Among the factors which determine the site of secondary rupture are a weakened outer wall, atheromatous plaques, and the presence of normal anatomic structures, such as aortic branches, which tend to hinder continued dissection.[1]

Dissecting aneurysm is frequently associated with hypertrophy of the left ventricle, which is presumably of hypertensive origin, or, less often, secondary to coronary atherosclerosis.[1, 7, 24, 28]

CASE REPORTS

In order to conserve space and avoid useless repetition, only positive findings are mentioned in the following case abstracts. In several instances the data are incomplete because the patients were admitted in such a serious condition or died so promptly that complete chemical and laboratory studies were impossible. Only necropsy material is included. The period which was surveyed extended from Jan. 1, 1929, to May 1, 1939.

CASE 1.—A colored man, 42 years of age, was admitted to Charity Hospital Nov. 3, 1930, and died a few minutes later, before any history could be obtained or a physical examination made.

Post-mortem examination revealed a dissecting aneurysm which extended over the entire length of the aorta, as well as between the serous layers of the parietal pericardium, with a secondary rupture into the pericardial cavity. Microscopic examination revealed atherosclerosis of the aorta.

CASE 2.—A white man, 62 years of age, was admitted to Charity Hospital June 20, 1932, and died three days later. Four hours before admission he had suddenly become dyspneic and had experienced severe retrosternal pain which radiated over the precordium. The pain had gradually disappeared, but residual tenderness was still present. The heart was enlarged, and an inconstant precordial thrill, associated with a murmur, was present. The blood pressure was 154/94. Three days after admission, when the patient was getting out of bed, he was seized with sudden, severe abdominal pain and died almost immediately.

Post-mortem examination revealed a primary, transverse tear of the aortic intima, which was located 9 cm. above the valve and reached two-thirds of the way around the circumference of the lumen. Proximal and distal dissection had extended over the entire length of the aorta, and a secondary rupture communicated with the pericardium. Other lesions included marked atherosclerosis of the aorta, calcification of the aortic valve, chronic glomerular nephritis, and an acute hemorrhagic ulcer of the stomach.

CASE 3.—A colored man, 40 years of age, was admitted to Charity Hospital Feb. 15, 1933, and died the following day. He was unconscious during the entire period of observation, and no history could be secured. The veins on the right side of the neck were markedly distended and pulsating, the heart was much enlarged, and a diastolic thrill and murmur were detected at the aortic area. The blood pressure was 110/80, and the spinal fluid Wassermann reaction was positive.

Post-mortem examination revealed a transverse, primary tear of the aortic intima, which was located 1 cm. above the semilunar valve and reached three-fourths of the way around the circumference of the lumen. Proximal and distal dissection had extended over the entire length of the aorta and the first portion of the left common iliac artery. A secondary rupture communicated with the pericardial cavity. The heart weighed 575 Gm.; the increase in weight was chiefly the result of hypertrophy of the left ventricle. Microscopic examination revealed typical syphilitic aortitis.

CASE 4.—A white man, 65 years of age, was admitted to Charity Hospital Feb. 15, 1933, and died eighteen hours later. Eight hours before admission he had been seized with sudden, severe epigastric pain, associated with dyspnea. Physical examination revealed a markedly enlarged heart, with occasional ectopic beats. The blood pressure was 190/110, and the blood Wassermann reaction was negative.

Fourteen hours after admission, the patient had a very severe attack of abdominal pain, followed four hours later by severe pain in the chest and dyspnea. The pulse was imperceptible, and the whole body was covered with profuse perspiration. Death occurred ten minutes after the second attack.

Post-mortem examination revealed a primary tear of the aortic intima at the junction of the ascending and transverse portions. Dissection of the media had proceeded distally from this point over the entire length of the aorta. A secondary rupture communicated with the left pleural cavity. Microscopic examination revealed thickening of the aortic intima and atherosclerosis.

CASE 5.—(This case has been reported elsewhere by Shattenberg and Ziskind.[16]) A colored man, 23 years of age, was admitted to Charity Hospital April 23, 1933, and died four hours later. Dyspnea, anasarca, and orthopnea had been present intermittently for a year. Three days before admission he had been seized with sudden, severe substernal pain, which had persisted. Physical examination revealed marked anasarca and dyspnea. The heart was very much enlarged, and a diastolic aortic thrill and murmur were present. The blood pressure was 140/40, and the blood Wassermann reaction was negative.

Post-mortem examination revealed a saccular dilatation of the ascending aorta. There was a primary intimal tear 2 cm. above the aortic valve, and intramedial dissection extended distally from it to the aortic bifurcation. A secondary rupture communicated with the pericardial cavity. Microscopic examination revealed medionecrosis cystica (Erdheim) and acute glomerular nephritis.

CASE 6.—A white man, 51 years of age, was admitted to Charity Hospital Nov. 5, 1934, and died ten hours later. He was in a state of shock when he was first seen, and he could give no history except that a few hours before admission he had experienced sudden, severe, persistent substernal pain, which was associated with loss of motion in the lower extremities. The initial blood pressure reading was 155/100; seven hours later the pressure had fallen to 80/68.

Post-mortem examination revealed a transverse, primary tear of the aortic intima, 3 cm. in length, at the junction of the arch and descending portion of the aorta. From this point, dissection extended proximally to the root of the aorta, where an extravasation of blood had elevated the auricular epicardium. Distal dissection extended throughout the aorta and into the first portion of the right iliac artery. Both iliac arteries, near their origin, were compressed almost to the point of complete occlusion. A secondary rupture communicated with the left pleural cavity. Both the right and left ventricles were moderately hypertrophied, and the deformation of the right and posterior semilunar cusps was such as to make the valve appear bicuspid. Congenital polycystic disease was present in both kidneys. Gross and microscopic examination revealed slight atherosclerosis in the ascending portion of the aorta and marked atherosclerosis of the abdominal portion.

CASE 7.—A white man, 59 years of age, was admitted to Charity Hospital Dec. 18, 1934, and died the following day. Three days before admission there had been a sudden onset of severe abdominal pain, which was persistent and was most intense in the left flank. The patient was very dyspneic.

Post-mortem examination revealed a primary tear of the aortic intima at the junction of the ascending and transverse portions of the arch. The dissection extended distally over the entire length of the aorta and into the first portions of both iliac arteries. A secondary rupture communicated with the lumen of the left iliac artery. A terminal rupture communicated with the mediastinum, and a large extrapleural hematoma was present on the right hemithorax. The left ventricle was markedly hypertrophied. Microscopic examination revealed a perivascular lymphatic and plasma cell infiltration of the vasa vasorum of the aorta.

CASE 8.—A white man, 52 years of age, was admitted to Charity Hospital Jan. 12, 1935, and died thirty-seven days later. He had been hospitalized several times previously because of hypertensive heart disease with congestive failure. On this admission he complained chiefly of dyspnea and edema of the legs and ankles. The

heart was moderately enlarged, and a loud systolic murmur was heard over the whole precordium. The blood pressure was 160/120, and the blood Wassermann reaction was negative. Urinalysis revealed albumin and epithelial casts. Electrocardiographic study showed left ventricular preponderance, a prolonged Q-T interval, and a wide P_2.

Eighteen days after admission, the patient suddenly developed severe substernal pain, became markedly dyspneic, and went into shock. A roentgenogram which was taken shortly after the anginal attack showed dilatation of the aortic arch. The pain and dyspnea persisted, and, five days before death, pure blood was aspirated from the left pleural cavity.

Post-mortem examination revealed a primary tear of the aortic intima at the junction of the ascending and transverse portions. Dissection of the media had taken place through the remainder of the aorta, and extended into the first portion of both common iliac arteries. A secondary rupture communicated with the left pleural cavity. Microscopic examination revealed atherosclerosis of the aorta and chronic glomerular nephritis.

CASE 9.—A white man, 49 years of age, was admitted to Charity Hospital March 21, 1935, and died forty-four hours later. He was in a state of shock, and no coherent history could be secured. He complained of severe abdominal pain, and, shortly after admission, had one tarry stool. The heart was slightly enlarged. The blood pressure was 150/95, and the blood Wassermann reaction was negative.

Post-mortem examination revealed a primary tear of the aortic intima just above the diaphragm. From this point, proximal and distal dissection of the media extended from the arch of the aorta to the bifurcation. A secondary rupture communicated with both the mediastinum and the left pleural cavity. The left ventricular wall was 7.5 mm. in thickness, and the heart weighed 300 Gm. Microscopic study revealed syphilitic mesaortitis.

CASE 10.—A colored man, 60 years of age, was admitted to Charity Hospital March 28, 1935, and died the following day. Three weeks before admission he had had sudden, severe, low dorsal pain, which had persisted until two days before he entered the hospital. Just before admission there had been a marked exacerbation of the pain, which radiated down the spine and over the abdomen. The patient had suffered from dyspnea and edema of the ankles for several years, and three years previously had developed right hemiplegia. Physical examination revealed residual manifestations of the old hemiplegia, moderate enlargement of the heart, and evidence of fluid in both pleural cavities. The blood pressure was 190/100.

Post-mortem examination revealed a primary tear of the aortic intima at the junction of the ascending and transverse portions. Just distal to the rent there was a localized dilatation, fusiform in character, which measured 4 cm. in diameter and was sharply demarcated from the adjacent lumen by a constricted ring formation. Intramedial distal dissection extended spirally over the entire length of the aorta and into the first portion of both common iliac arteries. A secondary rupture communicated with the left pleural cavity. There was gross evidence of both an atherosclerotic and a syphilitic process in the aorta. The heart was moderately enlarged.

CASE 11.—A white man, 28 years of age, was admitted to Charity Hospital July 12, 1936, and died three days later. Ten days before admission he had been seized with sudden, severe, penetrating pain in the left inframammary region, which radiated through the chest to the back. The pain had decreased in intensity within twenty minutes, but had never entirely disappeared. It was aggravated by deep breathing and was worse when the patient assumed the left lateral position. The heart extended to the left anterior axillary line, and an aortic diastolic thrill and loud aortic disastolic murmur were present. The blood pressure was 98/0.

Post-mortem examination revealed a small, primary tear of the aortic intima at the junction of the transverse and descending portions. Intramedial dissection extended from the point of the tear to the first portion of the abdominal aorta. A secondary rupture communicated with the left pleural cavity.

CASE 12.—A white woman, 38 years of age, was admitted to Charity Hospital July 17, 1936, and died seven days later. Four days previously she had been seized with a sudden, excruciating pain in the chest, which quickly extended to the toes. Later, there was impairment of motion in the lower extremities, which became numb and cold. The patient was bleeding from the vagina and was incontinent of urine.

Physical examination revealed no gross abnormality, except severe first-degree burns of the legs, which were the result of hot applications. A complete neurologic examination showed nothing abnormal. The blood pressure was 130/90, and both the blood and spinal fluid Wassermann reactions were negative.

Post-mortem examination revealed a primary intimal tear at the root of the aorta, and intramedial dissection extended over its entire length and into the first portion of both iliac arteries. An atherosclerotic process was present. The heart, which was markedly enlarged, weighed 500 Gm. The mitral valve was calcified and ulcerated, and the aortic valve was diffusely thickened. The pulmonic, splenic, and superior mesenteric arteries contained thrombi, and the small intestine was the seat of a beginning necrosis.

CASE 13.—A colored man, 37 years of age, was admitted to Charity Hospital April 24, 1937, and died twenty-four hours later. Three hours previously he had been suddenly seized with sharp epigastric pain associated with dyspnea, both of which had persisted. The previous history was irrelevant except for transitory edema of the ankles several months before. Scattered râles were present at the bases of both lungs, and the epigastrium was very rigid. The blood pressure was 130/80.

Post-mortem examination revealed a transverse, primary tear of the aortic intima, which was located 3 cm. above the aortic valve and involved two-thirds of the circumference of the lumen. A spiral intramedial dissection extended distally along the full length of the aorta and down the left iliac artery for a distance of 3 cm., resulting in obstruction of the innominate and left common carotid arteries. A secondary rupture communicated with the pericardial sac through a tear, 0.6 cm. in length, at the root of the aorta. The heart weighed 300 Gm. Microscopic study revealed syphilitic aortitis, but no evidence of atherosclerosis.

CASE 14.—A colored man, 65 years of age, was admitted to Charity Hospital July 9, 1937, and died August 13, 1937. For two weeks before admission he had had lower abdominal pain and dyspnea, and had had difficulty in starting urination. The urine had contained blood. Examination of the chest revealed dullness and râles at the bases of both lungs. The abdomen was slightly distended, and there was generalized abdominal tenderness. The prostate was markedly enlarged and tender. The blood pressure was 165/95.

Post-mortem examination revealed a primary rupture of the intima of the abdominal aorta through an atherosclerotic plaque. Intramedial dissection extended for a distance of 12 cm., at which point there was a secondary rupture into the aortic lumen. Examination of the kidneys and prostate revealed left-sided pyelonephritis and suppurative prostatitis.

CASE 15.—A colored man, 55 years of age, was admitted to Charity Hospital Jan. 27, 1938, and died in coma three days later. For three months before he entered the hospital he had suffered from dyspnea, orthopnea, and dependent edema. Five weeks previously he had been seized with sudden, agonizing pain in the left hypochondrium, which radiated to the precordium and to the right lower quadrant of the abdomen. The pain had recurred at intervals thereafter. Physical examina-

tion revealed a comatose patient, extremely dyspneic, with marked edema of the lower extremities. The left cardiac border was at the anterior axillary line, and there was a systolic murmur at the apex. The blood pressure was 216/160. The blood Wassermann reaction was negative. Urinalysis revealed both albumin and casts; the urea nitrogen content of the blood was 42 mg. per 100 c.c.

Post-mortem examination revealed coarctation of the aorta, just proximal to which a primary tear had occurred. An *old* dissecting aneurysm communicated with the lumen of the aorta. A recent secondary rupture, just proximal to the coarctation, communicated with the mediastinum. Examination of the kidneys revealed chronic glomerular nephritis.

CASE 16.—A white man, 62 years of age, was admitted to Charity Hospital May 5, 1938, and died four hours later. His chief complaints were abdominal cramps and bloody diarrhea.

Post-mortem examination revealed a primary, transverse tear of the aortic intima, 2.5 cm. in length, located 2.5 cm. above the aortic valve. Medial dissection extended over the entire length of the aorta and the first part of the superior mesenteric artery. The entire small intestine was gangrenous. Gross examination of the aorta revealed marked atherosclerosis.

CASE 17.—A white man, 61 years of age, was admitted to Charity Hospital Jan. 20, 1939, and died five days later. Thirty minutes before he had entered the hospital he had been seized with sudden, severe, restrosternal pain which radiated to the abdomen and was accompanied by marked cyanosis and dyspnea. For years the patient had had heart disease and had suffered from vertigo, dyspnea, and recurrent edema. Râles were heard at the bases of both lungs. The heart was moderately enlarged. The edge of the liver was palpable 6 cm. below the right costal margin. The blood pressure was 98/60. A slight leucocytosis was present. The sugar and nonprotein nitrogen content of the blood and the sedimentation time were within normal limits. The blood Wassermann reaction was strongly positive. Electrocardiographic examination showed left ventricular preponderance, with no evidence of coronary disease.

The second day after the patient was admitted the nonprotein nitrogen content of the blood had risen to 76.3 mg. per 100 c.c. Dyspnea increased progressively until death. The diagnosis of dissecting aneurysm was made ante mortem (L. F. H.).

Post-mortem examination revealed a marked, scattered atherosclerosis of the entire aorta. One of the plaques in the ascending portion had been partially elevated from the aortic wall and, from this point, intramedial dissection proceeded for a distance of 2 cm. The heart weighed 400 Gm. Microscopic examination revealed no disease of the media or of the vasa vasorum.

CASE 18.—A colored man, 46 years of age, was admitted to Charity Hospital March 23, 1939, and died suddenly twelve hours later. Several days previously he had been seized with sudden pain in the lower abdomen, which radiated into the right leg. At the same time, a mass which increased rapidly in size was noted in the region of the right femoral canal. The abdominal pain had subsided before admission, but the pain in the right leg was still present, and there was impairment of motion in this extremity.

Physical examination revealed a large, firm, tender, pulsating mass just inferior to the medial third of the right inguinal ligament. The right thigh and leg were cold and clammy, and the arterial pulsations were indistinct. The heart was slightly enlarged. Urinalysis was negative, as was the blood Wassermann reaction. The leucocyte count was 12,500, but there was no proportionate increase in the number of polymorphonuclear cells. A diagnosis of thrombosis of the right femoral artery was made, and a lumbar sympathetic block was done. Death occurred a few hours later.

Post-mortem examination revealed a primary, transverse tear of the aortic intima which was located 2.5 cm. from the valve and encircled the entire lumen. Dissection extended proximally and distally over the entire length of the aorta, and there were secondary ruptures into the right thigh, 7 cm. below the inguinal ligament, and into the pericardial sac. The left ventricle was hypertrophied, and the heart weighed 460 Gm. Microscopic examination revealed medial necrosis.

CASE 19.—A colored man, 34 years of age, was admitted to Charity Hospital April 16, 1939, and died three days later. Three days before admission he had been seized with sudden, severe, interscapular pain, which radiated to the coccyx and into the left leg. When the patient was brought to the hospital, there was complete loss of motion in this leg, and hematuria was present.

The heart was markedly enlarged to the left, and a to-and-fro murmur was audible in the aortic area. The left leg was cold and somewhat edematous, and the veins were distended. The pulsation of the left femoral artery was barely palpable. The blood pressure was 180/70 in the right arm, 170/64 in the left arm, 190/110 in the right leg, and 90/70 in the left leg.

The urine was grossly bloody, and contained a considerable amount of albumin (3 plus). The leucocyte count was 14,000, of which 82 per cent were neutrophiles. The blood Wassermann reaction was negative. Electrocardiographic examination revealed extreme left axis deviation; the QRS interval was 0.10 sec.; R_2 was slurred; T_1 was inverted; and the RS-T segment was depressed in Leads I and II. A teleoroentgenogram revealed dilatation of the ascending and transverse portions of the aorta, enlargement of the heart, and pulmonary congestion. An ante-mortem diagnosis of dissecting aneurysm of the aorta was made by the interne (Dr. J. M. Brocato).

Post-mortem examination revealed a primary, transverse tear of the aortic intima, 3 cm. above the aortic valve, with proximal and distal dissection throughout the entire length of the aorta. Secondary rupture had occurred into the pericardial sac. A large thrombus occluded the left iliac artery, and the right kidney was the seat of a large infarct.

DISCUSSION

An analysis of our own cases and of the cases in the literature makes it clear that the clinical manifestations of dissecting aneurysm are usually typical. The most characteristic feature is the sudden onset of severe thoracic or abdominal pain, which may remain confined to the trunk or may radiate to the lower extremities. In the latter respect, it differs from the pain of cardiac infarction, which frequently radiates down one or both upper extremities. A rapid extension of the pain from the thorax to the abdomen, and thence to the thigh, is probably to be explained by rapid dissection of the media in these regions. For this reason, a severe attack of thoracic pain, followed almost immediately by a severe attack of abdominal pain, is a sequence highly suggestive of dissecting aneurysm. The diagnosis of dissecting aneurysm is almost certain if, to this chain of events, there are added pain and impaired motion of the lower extremities, combined with weakness or absence of the arterial pulsations. The fact that the patient was apparently in good health before the attack of pain, or that the onset was not precipitated by exertion, should not be used as evidence against the possibility of dissecting aneurysm.

The aortic insufficiency which is commonly associated with dissecting aneurysm is apparently the result of a deformation of the aortic ring caused by the dissecting column of blood.[1] Its association with moderate or marked cardiac enlargement should not lead to the false assumption that the latter is a result of the former and, therefore, must have existed previous to the onset of the dissecting aneurysm. The aortic insufficiency, on the other hand, may indicate that secondary rupture of the aneurysm into the pericardial sac is impending.

Case reports which are lacking, as many of ours are, in serial microscopic examinations of the aortic wall add little to a clarification of the etiologic factors. Our survey of the literature and analysis of our nineteen cases have, however, crystallized our opinion as to certain aspects of the etiology, as follows:

A few patients with coarctation, or extreme hypoplasia, of the aorta are likely, because of these anomalies, to become victims of dissecting aneurysm. A few patients with atherosclerosis of the aorta may suffer ulceration of the intima, which permits dissection to begin at this point. Another relatively small group of patients develop dissecting aneurysms primarily because of disease of the vasa vasorum, of still unknown etiology, with secondary weakening of the media.

In the largest, and, therefore, the most important group of cases of dissecting aneurysm, none of these etiologic factors is present. Most patients, like those in our own series, present no specific disease of the aorta, although its absence can probably be explained in most cases by the fact that the microscopic examination was inadequate.

It is very unlikely that any bursting pressure within the aortic lumen could be of sufficient magnitude, in vivo, to cause rupture of the wall, unless some high-grade destructive process were present in the media. Many other observers are in agreement with us on this point. It is also clear, in view of what has already been said, that the postulated medial disease is necessarily unrelated to, and unlike, syphilis.

Considerable interest continues to center around the mechanics involved in the development of the initial linear tear of the intima. Inasmuch as none of the explanations which have so far been advanced appears to be acceptable, the following is offered by one of us (R. H. B.) because it explains many of the striking phenomena, and has, in our opinion, a reasonably sound theoretical basis.

The forces of stress at any point within the essentially elastic laminae of the aortic wall have a resultant magnitude equal to that of the effective internal pressure,[50] and their directions are tangential, or nearly tangenital, to the lamina at the point in question. It follows that rupture cannot take place in a direction normal to the wall, outward or inward. Furthermore, the stress will be maximal when dilatation is maximal, and the direction of the linear tear will be perpendicular to the

direction of the preponderant stretch. Consequently, a preponderantly longitudinal stretch will result in a circumferential tear, and a preponderantly dilating stretch will result in a longitudinal tear. When both of these varieties of stretch are equal, or nearly equal, in magnitude, the direction of the linear tear may be skew.

Thus, if we assume that there is a more or less diffuse medial disease, the majority of tears may be expected to occur in the ascending portion and arch of the aorta. Furthermore, since a longitudinal stretch is maximum in the ascending portion, the incidence of circumferential tears should be, and is, greatest here. The intima will rupture, of course, at the moment its limit of extensibility is exceeded, and since this limit is apparently less than that possessed by the outer lamina of the media, the rupture of the vessel wall is subtotal. Thus a situation suitable for dissection is established.

If these speculations are correct, a diligent search for disease of the media, other than syphilis, should be rewarded by the discovery of definite lesions in most, if not in all, of the large group of cases of dissecting aneurysm in which the etiology is not at once clear. In our own series, medionecrosis cystica was present in every case in which adequate studies were made.

SUMMARY AND CONCLUSIONS

1. All cases of dissecting aneurysm which have been reported in the American literature since 1933 have been collected, and nineteen new cases have been added.

2. The possible etiologic factors in dissecting aneurysm are analyzed, and the importance of medial necrosis is emphasized.

3. It is urged that a diligent search for medial necrosis be made in all cases of dissecting aneurysm in which the etiology is not at once obvious, for, in our experience, this condition has been found whenever adequate studies were made.

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Corrigendum

In the article entitled "The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients With Coronary Insufficiency," by Robert L. Levy, M.D., Howard G. Bruenn, M.D., and Norman E. Williams, M.D., which appeared in the June, 1940, issue of the Journal, the last sentence under Conclusion 4, on page 649, should read "The T waves were modified in seven of ten cases."

Department of Clinical Reports

NONINFECTIOUS THROMBOSIS OF A PATENT DUCTUS ARTERIOSUS

Report of a Case, With Autopsy

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PATIENTS with a patent ductus arteriosus frequently die of cardiac insufficiency or of infectious processes involving the heart. An unusual termination, resulting from occlusion of the superior mesenteric artery by emboli coming from a noninfected thrombus of a patent ductus arteriosus, deserves to be described. As far as can be ascertained, no similar case has been reported in an adult.

REPORT OF CASE

History.—A 55-year-old, white housewife was admitted to the Boston City Hospital a few hours after an attack of severe precordial pain, accompanied by difficulty in breathing. During this attack she lost consciousness, and fell and bruised her arms and hands. The patient had had hypertension for a number of years. For one year she had suffered from recurrent dyspnea and precordial pain. Prior to this time she had always been healthy and active. Two days before entry to the hospital she had increasing dyspnea, with severe headache and dizziness.

Physical Examination.—The patient was a well-developed, obese, drowsy woman, in no acute distress. Examination of the head and neck was negative. There were dullness and râles over the bases of both lungs posteriorly, and basal râles anteriorly. On percussion, the left border of the heart was within the anterior axillary line. The heart sounds were distant and the heartbeat was regular. There was no murmur or friction rub. The blood pressure was 150/100. Examination of the abdomen revealed no palpable organs or masses; there was no tenderness. Minimal edema of the ankles was present.

Laboratory Examinations.—At the time of entry, the total erythrocyte count was 4,800,000 per c.mm. The hemoglobin was 89 per cent (Sahli). The total leucocyte count was 20,900 per c.mm., with a differential count of 50 per cent polymorphonuclear leucocytes and 50 per cent lymphocytes. A blood Hinton reaction was negative. The nonprotein nitrogen content of the blood was 38 mg. per cent. The urine had a specific gravity of 1.025 Subsequent urine examinations during the period of hospitalization never showed any albumin or abnormal sediment.

An electrocardiogram on the first day showed normal sinus rhythm, with a rate of 81 per minute, a P-R interval of 0.16 second, and a QRS interval of 0.08 second. T_1 was inverted, and its origin was slightly high. T_2 was flat, T_3 upright, and T_4 inverted. The electrical axis was normal. The Q-T interval was 0.42 second. On the second day, T_2 became inverted, T_1, T_2, and T_4 were much deeper, and the Q-T interval was 0.64 second. The changes in the T waves were interpreted as suggesting the presence of an acute process. On the third day, the Q-T interval

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was 0.42 second, and the T waves were diminished in amplitude. On the sixth day there were only minor changes in the electrocardiogram.

Course of Illness.—The patient remained in the hospital for nine days. The day after entry she complained of weakness, associated with precordial pain which radiated to the left shoulder. The total leucocyte count at this time was 4,500, with a differential count of 75 per cent polymorphonuclear leucocytes and 25 per cent lymphocytes. During the course of the next five days she continued to complain of precordial pain and weakness. On the seventh hospital day there was a marked change in the patient's condition. She complained of extreme weakness and vomited several times. Severe precordial pain, which radiated into the back of the neck and shoulders, developed. Within an hour, this pain migrated to the abdomen. At the time of this attack the patient was pale and cold. There was profuse sweating. The blood pressure was 120/80. The total leucocyte count was 25,200 per c.mm., with a differential count of 92 per cent polymorphonuclear leucocytes and 8 per cent lymphocytes.

On the eighth day, pain was especially marked in the lower abdominal quadrants and was accompanied by vomiting. A small, bloody stool was passed. The total leucocyte count on this day was 24,300 per c.mm. On the ninth hospital day the pain in the abdomen was much more severe, and there were definite distention and rigidity, with generalized abdominal tenderness. No intestinal sounds could be heard. The pulse became rapid and weak. The patient went deeper into shock and died.

During the nine days of hospitalization the patient's temperature showed daily elevations to 99.5° F. The pulse rate, which was 90 per minute on the day of admission, fell to 70 on the second day, and continued at this level until the last hospital day, when it rose to 115 per minute. The respiratory rate during the entire period remained between 20 and 25 per minute.

Treatment was symptomatic. During the first six days the patient received morphine, codeine, and nembutal for relief of discomfort. During the last three days of life morphine and caffeine were administered.

The clinical diagnosis was coronary thrombosis, with mural thrombosis and mesenteric embolism.

Abstract of Autopsy Report.—Post-mortem examination was performed two and one-half hours after death. The anatomic diagnoses which were made at the time of autopsy were as follows: thrombosis of a patent ductus arteriosus, with an adjacent thrombus on the wall of the left branch of the pulmonary artery; thrombosis of the main trunk of the superior mesenteric artery, with infarction of the lower jejunum, entire ileum, cecum, and ascending colon; multiple, recent infarcts of the spleen; slight stenosis of the pulmonic valve; hypertensive heart disease, as indicated by moderate myocardial hypertrophy; and slight atherosclerosis of the aorta and pulmonary artery.

The heart was definitely enlarged, weighing 450 Gm. The left ventricular wall, which was moderately thickened, measured 1.5 cm., and the wall of the slightly thickened right ventricle measured 0.4 cm. The orifice of the pulmonary valve was small, measuring 5.5 cm., whereas the orifice of the aortic valve measured 7 cm. in circumference. The valves were otherwise normal and gave no evidence of healed or active inflammation. The walls of the coronary arteries were thickened, and they presented scattered, firm, yellow, intimal plaques. The lumina of the arteries were moderately narrowed.

A patent ductus arteriosus of the so-called funnel-shaped type was present. The broad, dilated portion opened into the aorta, whereas the narrow, stem-like portion opened into the left main branch of the pulmonary artery. The dilated, funnel-shaped portion of the ductus arteriosus measured 1.4 cm. in diameter and 1.3 cm. in depth. A short cylindrical passage, measuring 5 mm. in length and 4 mm. in diameter, extended from the apex of the funnel-shaped area into the left branch

of the pulmonary artery at a point 8 mm. beyond the bifurcation of the main stem. The walls of the funnel-shaped concavity were yellow, roughened, and calcified. Firmly attached to this roughened surface was a small red thrombus, with an uneven, granular surface. This thrombus, which measured approximately 5 mm. in diameter and incompletely filled the funnel-shaped portion, continued along the narrowed portion of the ductus arteriosus and projected into the lumen of the left branch of the pulmonary artery. Here it formed a soft, protruding mass which measured 6 mm. in diameter and was loosely adherent to the adjacent intimal surface of the pulmonary artery. The thrombus almost completely occluded the lumen of the narrowed portion of the ductus arteriosus. However, at the time of autopsy it was possible to pass a small, wire probe along the entire course of the ductus arteriosus without dislodging any portion of the thrombus.

Fig. 1.—Portion of heart, showing left ventricle, ascending aorta, and bifurcation of the pulmonary artery. Between the aorta and the pulmonary artery lies the patent ductus arteriosus, into which a probe has been inserted. An arrow indicates the thrombus overlying the pulmonary orifice of the ductus arteriosus.

The aortic arch measured 6 cm. in circumference just above the opening of the ductus arteriosus, and 5.6 cm. in circumference just below the opening. In the transverse portion of the aortic arch there was a single, noncalcified, atheromatous plaque, measuring 1.8 cm. in diameter. In the abdominal aorta, scattered, firm, yellow, intimal plaques, varying from 0.5 to 1.3 cm. in diameter, were present.

On the intimal surface of the main stem of the pulmonary artery there were several, slightly raised, pearly-gray, smooth elevations which varied from 3 to 6 mm. in diameter and did not exceed 1 mm. in height. The main stem of the pulmonary artery was not dilated.

The peritoneal cavity contained about 200 c.c. of watery, odorless, bloodtinged fluid. The peritoneal surfaces were smooth and glistening, although the external surface of the lower jejunum, entire ileum, cecum, and ascending colon exhibited a deep-red discoloration.

The pleural cavities contained no fluid, and their walls were smooth and glistening. The lungs were crepitant and not increased in weight. There was slight congestion of the lower lobes.

Fig. 2.—A portion of the wall of the ductus arteriosus has been removed, exposing the thrombus within its lumen.

The spleen was of normal size, weighing 100 Gm. On the capsular surface there were four or five, slightly bulging, grayish-yellow areas. Cut sections revealed a soft, dark-red pulp. Underlying each of the discolored areas of the capsule there was a firm, wedge-shaped area where the pulp was of a brownish-red color, presenting the appearance of red infarction. The splenic artery and vein showed nothing of interest.

The stomach, duodenum, and upper half of the jejunum showed nothing remarkable. The remainder of the jejunum, the entire ileum, the cecum, and the ascending colon had smooth, red, serosal surfaces. The walls of these segments of intestine were friable, and the mucosal surfaces were dark red. The lumen of

the discolored portion of the intestine contained a small amount of watery, dark-red fluid. The uninvolved lower portion of the colon and sigmoid contained a small amount of similar fluid. Six cubic centimeter beyond its origin, the main stem of the superior mesenteric artery was occluded by a soft, loosely adherent thrombus which extended distally for a distance of 5 cm.

The liver was of normal size, weighing 1,240 Gm. The parenchyma was slightly congested.

The kidneys were slightly reduced in size, weighing, together, 220 Gm. They presented smooth, light-brown surfaces, and slightly narrowed, irregular cortices which varied from 3 to 6 mm. in width. There were no infarcts or petechiae. The renal vessels showed nothing remarkable.

Microscopic Examination.—Five sections of the heart muscle were examined without finding evidence of extensive infarction. Scattered, small patches of myocardial fibrosis were seen. In several sections there were small areas in which the muscle fibers were intensely acidophilic and had a hyaline-like granular cytoplasm. Between some of the myocardial muscle fibers, in the perivascular connective tissue and beneath the endocardium, there were scattered small collections of cells consisting mainly of lymphocytes, with a few polymorphonuclear leucocytes, plasma cells, and macrophages. Nile blue and sudan IV stains revealed no fat in the muscle fibers.

Sections of the lungs showed moderate congestion of the alveolar septa, with small patches of bronchopneumonia, as indicated by small collections of polymorphonuclear leucocytes in the bronchioles and surrounding alveolar spaces. There were no vascular lesions.

Bland infarcts which were undergoing slight peripheral organization were present in the spleen.

The intestine showed changes which were consistent with early infarction. There was no evidence of peritonitis.

The lumen of the superior mesenteric artery was completely occluded by a thrombus which consisted of old fibrin, erythrocytes, and degenerating leucocytes. There were no leucocytes in the vessel wall, and there was no evidence of organization of the thrombus. No atheromatous changes were present in the intima.

A section of the ductus arteriosus, taken at the junction with the pulmonary artery, showed an attached thrombus which was undergoing extensive peripheral organization. Centrally, the thrombus was unorganized and consisted of old fibrin, degenerating erythrocytes, and poorly preserved leucocytes. The organized portion consisted of cellular fibrous tissue in which there were scattered small collections of lymphocytes, macrophages, and polymorphonuclear leucocytes. A second section, taken through the ductus arteriosus toward the pulmonary end of the vessel, showed an unorganized intimal thrombus. In this section, the underlying media contained small foci of polymorphonuclear leucocytes. Sections were not taken through the aortic end of the ductus arteriosus because it was desired to preserve the gross specimen. The media of the ductus arteriosus was composed of smooth muscle and hyalinized fibrous tissue. The intima was slightly thickened and hyalinized. There were no areas of necrosis in the vessel wall.

Sections through the pearly elevations in the pulmonary artery revealed intimal, hyalinized masses which contained small amounts of atheromatous material.

In the kidney sections there were no evidences of toxic or embolic manifestations. The larger vessels showed a moderate degree of arteriosclerosis.

The liver showed slight central congestion.

Sections of the other organs showed nothing remarkable.

Bacteriologic Examination.—A post-mortem culture of the heart's blood remained sterile. A culture of the peritoneal exudate at autopsy yielded *B. coli*, *Staphylococcus aureus*, and a streptococcus with alpha prime hemolysis. At the time of

autopsy, no culture was made of the thrombus in the ductus arteriosus. Bacterial stains (MacCallum-Goodpasture and Gram-Weigert) were made on sections of the heart muscle, on sections of the ductus arteriosus containing the thrombus, on the thrombosed superior mesenteric artery, and on two of the splenic infarcts. In no instance could any bacteria be demonstrated.

DISCUSSION

The extensive organization of the thrombus lying in the ductus arteriosus suggested that it was at least several weeks old. There was nothing in this thrombus to indicate that it was of infectious origin. The splenic infarcts were undergoing early organization and appeared to be younger than the thrombus lying in the ductus arteriosus. These infarcts were not suppurative in nature. The unorganized thrombus in the superior mesenteric artery was still more recent, which was consistent with the duration of the abdominal symptoms. The microscopic lesions in the myocardium could be attributed to focal areas of circulatory insufficiency.

At the time of the patient's admission to the hospital the ductus arteriosus was probably already occluded by a thrombus—a fact which would explain the absence of a cardiac murmur. In an attempt to secure additional evidence of impaired function of the heart, the patient's husband was interviewed. He did not know whether or not his wife had had a cardiac murmur. He stated that she had always been well and active until the preceding year, when she had begun to complain of dizziness and "ringing in the ears." The family physician, who had been treating the patient for "high blood pressure" for about five years, did not recollect whether or not the patient had had a heart murmur. Such observations would indicate that we were dealing with a functionally insignificant ductus arteriosus. This was supported pathologically by the absence of significant right ventricular hypertrophy and by the absence of dilatation of the pulmonary artery. The pulmonary atherosclerosis which was observed in this case is frequently associated with patency of the ductus arteriosus.

Patency of the ductus arteriosus is a rare occurrence in adults. White[1] states that only seven cases were encountered, excluding infants under 1 year of age, in 5,000 consecutive autopsies at the Massachusetts General Hospital. Abbott[2] found this condition in eighty-four of a series of 850 cases of cardiac defects.

In the literature, there are reports of thirty-five, or more, cases of infective vegetations occurring in a patent ductus arteriosus in which the diagnosis was confirmed at autopsy. Many others have been reported without post-mortem examination. Schlaepfer,[3] in 1926, collected a series of nineteen cases and presented an additional case. Blumer and McAlenney,[4] in 1931, collected a series of twenty-eight similar cases and added six of their own, in two of which the patient came to autopsy. More recently, five additional cases have been reported.[5-9]

In these thirty-five cases of septic thrombosis of a patent ductus arteriosus, the following features seem worthy of note. In only five of the thirty-five instances were the heart valves intact.[3, 4, 9] The tricuspid valve seems to be the least likely site of the valvular endocarditis which is so often associated with infectious lesions of the ductus arteriosus. Congenital defects of the heart itself are uncommon in this condition. The adjacent pulmonary artery is frequently involved in the inflammatory process. Pulmonary infarcts are common. The clinical course and symptoms are similar to those in cases of endocarditis without involvement of a ductus arteriosus. The *Streptococcus viridans* was most frequently responsible for the infection.

In the case reported here, there was nothing to suggest an infectious process involving the ductus arteriosus. The short duration of the symptoms, the good nutrition of the patient, the absence of marked anemia and of petechiae, the slow pulse rate, and the relatively afebrile course are uncommon in cases of endocarditis or septic arteritis. Pathologically, the lack of splenic enlargement, the absence of cardiac valvular involvement, and the histologic appearance of the thrombi and of the infarcts, in addition to the fact that the kidneys were normal, support the contention that the thrombosis of the ductus arteriosus was noninfectious. Moreover, bacterial stains on sections of the thrombi, the heart muscle, and the splenic infarcts revealed no organisms.

Thrombosis of a patent ductus arteriosus of a noninfectious type is far less common than that caused by infection. Kowalski[10] described the case of a well-developed, full-term infant who collapsed on the sixth day of life and died two days later. The infant was found to have thrombosis of the ductus arteriosus, with emboli to the renal arteries, and cerebral ischemia. Kowalski reviewed six similar cases, all of which occurred in infants under 2 weeks of age. More recently, Bettinger[11] reported a similar case in a normal infant who died on the tenth day of life.

As far as can be ascertained, there is no reported case of noninfectious thrombosis of a patent ductus arteriosus in an adult. Altschule[12] described the case of a 57-year-old man who died of cardiac failure. At autopsy, a marked sacculation was found in the aorta at the site of the ductus arteriosus. The sacculation was thought to be an aneurysmal dilatation of a ductus arteriosus which was closed on the pulmonic side. The only systemic embolus which was found was an organizing thrombus in one medium-sized pancreatic artery.

The calcified plaque which was present in the funnel-shaped opening of the ductus arteriosus in our case is significant, for it is likely that the thrombus originated on the surface of this rough plaque and then spread into the narrowed portion of the ductus arteriosus. Weiss[9] states: "In communication, Dr. M. E. Abbott informs me that in her series of 90 cases of patent ductus arteriosus, calcific deposits at the aortic end

of the ductus were observed in only two cases.'' He added a similar case which occurred in a 33-year-old woman with a septic thrombus of the ductus arteriosus and the adjacent pulmonary artery.

Recently, we have observed the frequency with which atheromatous plaques occur in the aortic arch at the site of the ligamentum arteriosum. In fifty autopsies on adults in which this area was examined, calcified plaques were present in the aorta at this site in twenty-nine instances. Noncalcified plaques were present in nine instances in this same region. Other, and, at times, larger, atheromatous lesions were frequently present in the aortic arch. The age of the patients varied from 30 to 85 years. The majority were in the sixth and seventh decades. The apparent predilection for calcification in this portion of the aortic arch should favor thrombus formation in cases of patency of the ductus arteriosus.

SUMMARY

An elderly woman was admitted to the hospital following an attack of severe precordial pain. On the seventh hospital day she developed abdominal pain which continued until her death, two days later. Postmortem examination disclosed embolic occlusion of the superior mesenteric artery. The embolus arose from fragments coming from a recently thrombosed patent ductus arteriosus. The clinical, pathologic, and bacteriologic observations indicated that the thrombus was not infectious in origin.

REFERENCES

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2. Abbott, M. E., and Weiss, E.: The Diagnosis of Congenital Heart Disease, Philadelphia, 1928, W. B. Saunders Co.
3. Schlaepfer, K.: Chronic and Acute Arteritis of Pulmonary Artery and of Patent Ductus Arteriosus, Arch. Int. Med. 37: 473, 1926.
4. Blumer, G., and McAlenney, P.: Relationship of Patent Ductus Arteriosus to Infectious Process in Duct Itself, in Pulmonary Artery, Aorta and Heart Valves, Yale J. Biol. & Med. 3: 483, 1931.
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6. D'Aunoy, R., and von Haam, E.: Aneurysm of Pulmonary Artery With Patent Ductus Arteriosus; Report of 2 Cases and Review of Literature, J. Path. & Bact. 38: 39, 1934.
7. Perry, C. B.: Patent Ductus Arteriosus With Superimposed Subacute Bacterial Endocarditis, Lancet 1: 82, 1933.
8. Hines, D. C., and Wood, D. A.: Patent Ductus Arteriosus Complicated by Endocarditis and Hemorrhagic Nephritis; Case Report, Am. Heart J. 10: 974, 1935.
9. Weiss, E.: Calcified Plaque of Aorta at Entrance of Patent Ductus Arteriosus: Point in Diagnosis, Am. Heart J. 7: 114, 1931.
10. Kowalski, W.: Über Thrombose des Ductus Arteriosus bei Neugebornen, Virchows Arch. f. path. Anat. 233: 191, 1921.
11. Bettinger, H.: Beiträge zur Pathologie des Ductus Botalli, Centralbl. f. allg. Path. u. path. Anat. 54: 289, 1932.
12. Altschule, M. D.: Aneurysm of Arch of Aorta Due to Persistence of Portion of Ductus Arteriosus in Adult, Am. Heart J. 14: 113, 1937.

Department of Reviews and Abstracts

Selected Abstracts

Moia, B., and Battle, F. F.: Characteristics of the Hepatic Pulse in Cases of Coincidental Auricular and Ventricular Contractions. Rev. argent. de cardiol. 7: 31, 1940.

Optical records of hepatic pulse were obtained by means of Frank's segment capsule simultaneously with other records (electrocardiogram, venous pulse, apex beat, central arterial pulse, heart sounds), in sixteen patients with disorders of rhythm in which there occurred a coincidence of auricular and ventricular contractions.

When the conditions for its recording were favorable, the hepatogram showed, each time auricular and ventricular systoles coincided, a well-marked systolic wave. *This wave is due to a reflux determined by the mechanically blocked auricular contraction* (Wenckebach's *vorhofspfropfung*). The important role of this mechanical block in the origin of the circulatory disturbances observed in these cases is thus confirmed.

AUTHORS.

Sugarman, H., Katz, L. N., Sanders, A., and Jochim, K.: Observations on the Genesis of the Electrical Currents Established by Injury to the Heart. Am. J. Physiol. 130: 130, 1940.

The electrical changes produced by an area of injury on the dog's ventricle were studied in two types of experiments. In the first type, a very small injured area was produced by pressure, and by means of a unipolar lead from this spot, it was found that as the injury is produced, the spot becomes negative when the heart is at rest and positive during complete cardiac activation, measured with respect to the potential of normal uninjured cardiac muscle. These changes disappear on recovery from the injury. This observation confirms the recent results of Eyster, Meek, et al.

In the second type of experiment, a small area of injury was produced by intramyocardial injection of 95 per cent alcohol, and, by means of unipolar leads, the potential changes with time were followed in the injured area and at points on the ventricles at different distances from the center of injury. The results were:

1. Changes in the contour of the QRS complex, indicating an alteration in the pattern of impulse spread, occurred in the injured area and later also in other areas outside this region.

2. A depression of the S-T level occurred, which was maximum in the injured region and became smaller out toward the periphery. These changes tended to disappear with time.

3. A coronary type of upright T wave appeared some time after the injury was produced and was confined to the margin of the injury and a narrow region surrounding it. This T wave tended to disappear with time.

An explanation of the results of both types of experiment is offered on the basis of the classical membrane theory.

The change in contour of the QRS produced by injury is ascribed to alteration in the pattern of impulse spread.

The T-Q elevation and S-T depression are attributed to the production by injury of a region which is partially depolarized at rest, and irresponsive duration activation.

The late appearance of the large upright "coronary" T wave is ascribed to the production outside the original area of injury of a partially injured region which responds normally to activation, but which lags temporarily behind normal tissue in the process of repolarization.

AUTHORS.

Hertzman, Alrick B., and Dillon, John B.: Distinction Between Arterial, Venous and Flow Components in Photoelectric Plethysmography in Man. Am. J. Physiol. 130: 157, 1940.

This paper studies the possibility of distinguishing "active" from "passive" components, of separating arterial from venous reactions in photoelectric plethysmograms of the human skin.

A technique is described for recording the volume pulse separate from the plethysmogram, with a photoelectric plethysmograph and capacity couple amplifier.

The arterial component in the plethysmogram is distinguished by the amplitude of the volume pulse.

The flow component is indicated by the product, amplitude of the volume pulse × heartrate. The value of this product appears to parallel flow.

The analysis of the volume changes recorded in the plethysmogram involves evaluating the arterial and flow components by these criteria and so by a process of exclusion, differentiating when possible the contribution of the venous component.

Measurement of the venous pressure in the finger pad by obstructing the return with a Gärtner capsule indicates a surprisingly high venous pressure in the pad and also a high venous tone there.

Evidence is presented which seems to show that moderately heavy doses of amyl nitrite produce prolonged loss of venous tone.

AUTHORS.

Parkinson, John: Cardiac Examination in Wartime. Brit. M. J. 1: 428, 1940.

The recognition of heart disease in men of military age is to be approached more on the basis of physical signs than that of symptoms. The work of a medical examiner in wartime is difficult enough and constant care must be used to prevent the occasional acceptance of a cardiac subject with slight heart disease. The physical signs will often be slight or dubious, and difficult to interpret. A shaky sign is a poor foundation for a weighty diagnosis though this may rest on a trusty sign supported by others less convincing. The author proceeds to recapitulate and examine these signs as they apply to the recognition of the early stage or minor grades of cardiac disease in recruits and soldiers.

He emphasizes the importance of the case history of rheumatism or signs of a congenital anomaly during early childhood, and the importance of pulse rate, the character of the apex beat, the cardiac size, and signs of auscultation of altered heart sounds and murmurs. He stresses the importance of signs of congenital heart disease at this period of life.

MCCULLOCH.

Mulinos, Michael G., and Shulman, Israel: The Effects of Cigarette Smoking and Deep Breathing on the Peripheral Vascular System. Am. J. M. Sc. 199: 708, 1940.

Using five different methods, an analysis of the response of the peripheral vascular system to smoking and to deep breathing led the authors to conclude that deep breathing alone can account for the greater part of the decrease in rate of flow, loss of hand volume, and drop in skin temperature resulting from the inhalation of cigarette smoke. Denicotinized cigarettes caused as great and occasionally greater vasoconstriction than inhaling smoke from a standard brand cigarette.

SCHWARTZ.

Garvin, Curtis F.: Functional Aortic Insufficiency. Ann. Int. Med. 13: 1799, ***Advanced Hypertensive Disease and Chronic Glomerular Nephritis.*** Am. J. M. Sc. 200: 39, 1940.

A peculiar type of myocardial degeneration appears to be intimately associated with the uremic and preuremic states of arteriolar nephrosclerosis and chronic glomerular nephritis. It is found especially in those patients who have cardiac failure. The latter may be the outstanding feature of uremic intoxication. Pericarditis may be regarded as a complication of this myocardiopathy.

AUTHOR.

Garvin, Curtis F.: Functional Aortic Insufficiency. Ann. Int. Med. 13: 1799, 1940.

A survey of 200 consecutive autopsied cases of hypertensive heart disease discloses fourteen cases in which a diastolic murmur was heard at the base of the heart. This finding led to varying degrees of difficulty in clinical interpretation. In four instances a frank error in etiologic diagnosis was made. At autopsy the heart in these cases was dilated but showed perfectly normal valves. In fact, the pathologic findings permitted no other conclusion than that the aortic insufficiency noted in life was functional and not due to anatomic changes in the valve leaflets.

It is thought that functional aortic insufficiency occurring in cases of hypertensive heart disease is more common and more important than is generally recognized.

AUTHOR.

Hoff, Alfred: Some Clinical Vagaries Associated With Bacterial Endocarditis. Minnesota Med. 23: 25, 1940.

This paper is a clinical review, including necropsy findings in thirteen cases of bacterial endocarditis.

These cases have been classified according to their presenting symptoms and signs on admission to the hospital.

Embolic manifestations concealed in deep structures may dominate the clinical picture of this disease.

As a result, one may fail to make the correct diagnosis, which comes as a surprise finding at necropsy.

AUTHOR.

Altschule, Mark D., and Budnitz, Edward: Rheumatic Disease of the Tricuspid Valve. Arch. Path. 30: 7, 1940.

The clinical syndrome of rheumatic disease of the tricuspid valve is characterized by distention and increase in diameter of all visible veins, hepatomegaly, systolic (and in the absence of auricular fibrillation, presystolic), venous and hepatic pulsations, cyanosis, jaundice, enlargement of the heart to the right and murmurs over the area of the tricuspid valve. The clinical evidence of cirrhosis of the liver or of congestive heart failure may complicate the picture. The special pathologic condition causing this syndrome consists in insufficiency and variable degrees of stenosis of the tricuspid valve, dilatation of the right auricle and of the veins and cirrhosis of the liver. The cardiac output is normal when congestive failure is not present. Nevertheless, the venous pressure is elevated, proving that the rise in venous pressure is due to mechanical obstruction to the heart's inflow of blood. When cardiac decompensation occurs, the output of the heart diminishes, and the venous pressure rises above its former high level. The relation of the pathologic and physiologic features of the syndrome to its clinical manifestations is discussed in detail.

AUTHORS.

Bennett, Granville A., Zeller, J. Wallace, and Bauer, Walter: Subcutaneous Nodules of Rheumatoid Arthritis and Rheumatic Fever. Arch. Path. 30: 70, 1940.

The nodules of rheumatoid arthritis and rheumatic fever differ as much from one another as do the granulomas of syphilis and tuberculosis, suggesting that they may be due to different agents. The clinical and pathologic differences of rheumatoid arthritis and rheumatic fever also favor such an interpretation. It is, therefore, suggested that the readily accessible subcutaneous nodules should be studied by new and untried methods in the hope that more may be learned concerning their genesis and cause. The present study has yielded information that should be useful in differential diagnosis.

AUTHORS.

Rathe, Herbert W.: Rheumatic Heart Disease. J. Iowa M. Soc. 30: 95, 1940.

The author presents the conventional story of rheumatic fever and its relationship to heart disease. He emphasizes that rheumatic fever is a disease of the heart; it may be insidious in its development but once developed, the patient should be considered as having a crippled heart.

There is an analysis of 650 cases of organic heart disease observed in an Iowa clinic. Of these, ninety-five cases were due to rheumatism. These cases were arranged in tables for statistical analysis of rheumatic activity, sex, type of pathologic change in the heart, and course of the disease.

McCULLOCH.

Plant, Alfred: Hemangioendothelioma of the Lung. Report of Two Cases. Arch. Path. 29: 517, 1940.

A case is reported of multiple intravascular hemangioendothelioma of the lung connected with widespread structural abnormalities of the pulmonary arteries. There was also a capillary angioma of the involved lung, and a large defect of the interventricular system. A second case of pulmonary endothelioma is briefly described.

The different forms of tumors arising in pulmonary vessels are described from the literature, and their interrelations and genesis are discussed.

SCHWARTZ.

Roesler, Hugo, Gibson, Glen G., and Hussey, Raymond: A Correlation Study Between Retinal Vascular Changes, Electrocardiographic Alterations and Radiological Heart Size in Essential Hypertension. Ann. Int. Med. 13: 1814, 1940.

Eighty carefully selected cases of essential hypertension were studied from the point of view of retinal vascular changes and electrocardiographic alterations, and fifty-nine of them as to radiologic heart size, and a correlation between these criteria was carried out.

Retinal vascular changes were noted in all of the selected cases, with 88.8 per cent graded as sclerosis, hypertensive type. The electrocardiogram revealed final deflection changes in 68.8 per cent. A slight to moderate enlargement of the heart was noted in 50.8 per cent, and a marked degree in 27.1 per cent.

There is a trend toward a positive correlation between electrocardiographic alterations and the grade of the retinal arteriolar changes, between cardiac enlargement and the grade of the retinal arteriolar changes, and between electrocardiographic alterations and the degree of cardiac enlargement. This correlation was not demonstrated to be of high statistical significance.

Some of the possible causes for this incomplete correlation are discussed, among which the irregular distribution of the vascular processes and the lack of strict parallelism between the systemic and central retinal artery blood pressure are stressed.

Inasmuch as there is an inadequate correlation between the three criteria in question, it seems desirable to have, in a given case of essential hypertension, an evaluation of the eyeground, electrocardiogram, and heart size, in addition to the more routine studies, when one attempts the difficult task of making a practical prognosis for a patient who has this disease.

AUTHORS.

Van Epps, E. F., Hyndman, O. R., and Greene, James A.: Clinical Manifestations of Paroxysmal Hypertension Associated With Pheochromcytoma of Adrenal. Arch. Int. Med. 65: 1123, 1940.

The manifestations of paroxysmal hypertension due to an adrenal medullary tumor are discussed and the diagnostic aids are emphasized. It is believed that such paroxysmal hypertension is usually curable if it is diagnosed before an irreparable vascular damage has occurred. One case of proved and one of doubtful pheochromocytoma are reported.

MCCULLOCH.

Allen, Philip D.: Periarteritis Nodosa Simulating an Acute Abdominal Condition Requiring Operation. Arch. Surg. 40: 271, 1940.

A case is reported in which the patient was operated on for a penetrating peptic ulcer; exploration revealed no evidence of ulcer but an apparently chronic cholecystitis. A cholecystectomy and an appendectomy were performed, and material for biopsy was removed from the liver. Pathologic examination of the specimens revealed the changes in the gall bladder to be due to a disease of the blood vessels supplying it, namely, periarteritis nodosa. The outstanding clinical and pathologic features of the disease are discussed. Emphasis is placed upon the frequency with which periarteritis nodosa is incorrectly diagnosed as a lesion requiring surgical intervention.

AUTHOR.

Smithwick, R. H.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease. Arch. Surg. 40: 286, 1940.

Sympathectomy yields its most satisfactory clinical results when it is performed in such a way that the area is completely denervated by a preganglionic procedure. It is important also that the operation be performed in such a manner as to guard against regeneration.

The most brilliant results are obtained in cases of purely vasospastic disorders. However, worth-while improvement may often follow if sympathectomy is performed when both obliteration and spasm of arteries are known to exist.

Various methods of testing for vasospasm are discussed. The value of studying reflex vascular and sweat gland activity is emphasized, particularly with regard to determining both the completeness and the permanence of the results of any operative procedure. The importance of clinical observation and judgment based on experience is mentioned in connection with the selection of cases for operation.

Various changes which take place after sympathectomy are considered in some detail. The difference between complete and incomplete sympathectomy is brought out. The question of "relapse" due to partial regeneration of sympathetic pathways is discussed with particular reference to reflex vascular and sweat gland activity.

The operative technique which has been found to produce the most satisfactory denervation of both upper and lower extremities is described briefly.

Clinical results in cases of both primary and secondary vasospastic disorders are tabulated. The results in various surgical measures utilized in the management of patients with thromboangiitis obliterans are discussed in terms of the incidence of major amputations.

AUTHOR.

Murray, Gordon: Heparin in Surgical Treatment of Blood Vessels. Arch. Surg. 40: 307, 1940.

In 440 patients in the hospital treated with heparin, thrombosis and embolism did not occur. Patients with thrombophlebitis were thought to be improved by treatment. Striking improvement was observed in a group of patients with pulmonary embolism; with one possible, but unproved, exception, none of these patients had further embolisms, and none died of pulmonary embolism. Embolectomies were successful in twelve cases when heparin was used. In one case a venous graft was placed in an artery; this remained patent and functioned satisfactorily. It is suggested that heparin is a most important agent for prevention of thrombosis when operation for repair of blood vessels is undertaken. Heparin might also be used to advantage for disease in which thrombosis and clotting in the blood vessels occur.

AUTHOR.

Freeman, Norman E.: Influence of Temperature on the Development of Gangrene in Peripheral Vascular Disease. Arch. Surg. 40: 326, 1940.

Gangrene results from a discrepancy between the demands of the tissues and the supply of blood to meet these nutritional needs.

Experimental investigations of the effect of temperature on the volume flow of blood through sympathectomized extremities indicate that the circulation is conditioned by the metabolic requirements of the tissues.

The metabolism of the tissues increases directly with the temperature.

In the presence of organic occlusive vascular disease, the application of unregulated heat may precipitate gangrene, since it may increase the metabolism of the tissues more than it increases the circulation.

Use of a thermoregulated cradle of simple construction is suggested in order to maintain the environmental temperature at the desired level.

AUTHOR.

Herrmann, Louis G., and McGrath, Edward J.: Effect of Estrogens on Vascular Spasm Due to Active Angiitis in the Extremities. Arch. Surg. 40: 334, 1940.

A total of sixteen patients with marked secondary vasoconstriction associated with active angiitis in the extremities has been studied and then given estrogens as the primary therapeutic agent. In this review of our experiences, an attempt has been made to present our interpretation of the benefits which have resulted after a careful analysis of the patient's account of the subjective benefits, together with the objective evidence of importance which we have gathered from repeated vascular studies. It must be emphasized that three patients of this series who had active thromboangiitis obliterans have returned after several years with reactivated acute angiitis.

The cholinergic effect of the estrogenic substances appears to supply only a partial explanation of these clinical results. What other effects may be exerted on the diencephalic vasomotor centers through the primary effect of the estrogenic substances on pituitary function is a problem for further study. It is a clinical fact, however, that all patients do not react alike to these substances, and the apparent difference between the reaction of the male organism and that of the female organism might be explained on the basis of less intense action on the central vasomotor centers.

AUTHORS.

Kvale, Walter F., Smith, Lucian A., and Allen, Edgar V.: Speed of Blood Flow in the Arteries and in the Veins of Man. Arch. Surg. 40: 344, 1940.

The methods of study which we have used indicate that the speed of the flow of blood in the arteries and in the veins of the extremities is influenced by a number of factors. Chronic occlusive arterial diseases usually slow the arterial circulation, but they do not always do so. Hyperthyroidism increases the speed of blood flow; hypertension slows it in the lower extremities; sympathectomy speeds it greatly, as does increasing the temperature of the skin of the digits. Elevation of an extremity increases the speed of flow of venous blood, but when the subject stands the speed of flow of arterial blood is decreased. Digestion is associated with an increase in speed of blood flow, and exercise accelerates flow in arteries and veins. Operation usually reduces the speed of the flow of blood in the veins of the lower extremities.

AUTHORS.

McKittrick, Leland S.: Diabetic Gangrene. Review of 972 Cases of Gangrene Associated With Diabetes Mellitus Treated at the New England Deaconess Hospital. Arch. Surg. 40: 352, 1940.

The organization at the New England Deaconess Hospital for the care of patients with diabetes mellitus and a gangrenous lesion of an extremity is described.

Nine hundred and seventy-two cases of obliterative vascular disease in patients with diabetes mellitus are reviewed.

The sex distribution was about equal. The average age was 64.3 years. The average duration of diabetes was eight and seven-eighths years. The mortality in the hospital was 9.4 per cent. The mortality after major amputation was 13.9 per cent.

The causes of death in seventy-three fatal cases are discussed.

A comparison is given of the results following the use of silk and catgut sutures in 112 consecutive primary supracondylar amputations.

The cases of one hundred consecutive patients who left the hospital after a major amputation for gangrene have been followed. The incidence of gangrene of the other extremity, the survival rates, and the average postoperative duration of life are given.

The end results in the cases of thirty-three patients who left the hospital after refusing amputation are given.

AUTHOR.

Green, Harold D., and Gregg, Donald E.: Changes in the Coronary Circulation Following Increased Aortic Pressure, Augmented Cardiac Output, Ischemia and Valve Lesions. Am. J. Physiol. **130:** 126, 1940.

Records of the moment-to-moment rates of flow and of the total inflow into the left coronary artery of dogs have been taken with the orifice meter together with the aortic and peripheral coronary pressures under different dynamic conditions. Study of such indicates that during both systole and diastole the total and intramural flows increase following aortic compression, blood transfusion, ischemia and aortic insufficiency (only during systole), while in diastole of the latter the intramural flow decreases and the total flow increases. The pressure differentials follow in the direction of the metered flows but since they change much less they can provide only a qualitative measure of flow. These differential pressure changes may be less than, greater than, or the same as the flow alterations.

The latter findings permit certain deductions, provided one subscribes to the idea previously advanced that changes especially during diastole, in the ratio of intramural flow to differential flow may indicate alterations in size of the available coronary bed, and in addition that changes in systolic peripheral coronary pressure reflect changes in extravascular compression or support.

Calculations made upon this basis indicate that following increase of cardiac work through simple elevation of aortic pressure the available coronary bed becomes smaller while in ischemia and in augmented cardiac work due to increased cardiac output the bed increases, because in the former the diastolic flow increases less than the pressure differential while in the latter the reverse is true. Substantiating this is the observation that the minute flow per millimeter Hg aortic pressure decreases with aortic compression and increases with augmented venous return.

In elevation of aortic pressure, augmented cardiac output, aortic stenosis and aortic insufficiency, but not ischemia, the extravascular support is presumably increased as evidenced by the increased peripheral coronary systolic pressure. However, failure of such increase in extravascular compression to rise concomitantly with the aortic systolic pressure is in part responsible for the augmentation of systolic flow in these conditions and its converse for the reduction of flow in aortic stenosis.

AUTHORS.

Schlesinger, Monroe J.: Relation of Anatomic Pattern to Pathologic Conditions of the Coronary Arteries. Arch. Path. 30: 403, 1940.

The coronary artery pattern is not the same in all its details in any two human hearts. These multitudinous variations can be classified into three definitely different, distinctive anatomic and functional groups. In group I, comprising 48 per cent of human hearts, the right coronary artery predominates in the blood supply of the heart; these hearts are intermediate to the other two groups in their reaction to the ravages of coronary arteriosclerosis. In group II, comprising 34 per cent of human hearts, the coronary artery blood supply of the heart is balanced between the right and left coronary arteries; these hearts suffer the least from the effects of coronary arteriosclerosis. In group III, comprising 18 per cent of human hearts, the left coronary artery predominates in the blood supply of the heart; these hearts suffer the most from the effects of coronary arteriosclerosis.

AUTHOR.

Veal, J. Ross: Thrombosis of the Axillary and Subclavian Veins. With a Note on the Post-Thrombotic Syndrome. Am. J. M. Sc. 200: 27, 1940.

The symptom complex of thrombosis of the axillary and subclavian veins is reviewed. A classification and examples of the various types of thrombosis are given. Clinical studies from seventeen cases are recorded.

The frequency of secondary thrombosis from malignancies of chest and axilla is emphasized. The development of collateral circulation after occlusion of the axillary and subclavian veins is discussed. An explanation of the post-thrombotic syndrome, based on the inadequate collateral circulation and elevation of the local venous pressure, is offered. A résumé of treatment for the various forms of thrombosis is outlined.

AUTHOR.

Culp, Ormond S.: Postoperative Venous Thrombosis and Pulmonary Embolism. Bull. Johns Hopkins Hospital 67: 1, 1940.

During the past twenty years 6.62 per cent of all the postoperative deaths on the urologic service were due to proved fatal pulmonary embolism. All of the 8,163 operations performed during the same period have been reviewed and eighty-eight cases of postoperative pulmonary embolism found. These included five types of cases: A, proved fatal embolism (32), B, presumptive fatal embolism (11), C, pulmonary infarcts with recovery (21), D, infected pulmonary infarcts (4), and E, incidental pulmonary infarcts (20).

Eight additional cases of fatal pulmonary embolism, proved by autopsy, occurred in patients who had not been subjected to operation.

Each group of cases has been analyzed in an attempt to determine the contributing factors. Several prophylactic measures have been recommended.

In most instances, the predisposing venous thrombosis was not diagnosed clinically. Several patients were subjected to operation or allowed out of bed in the presence of unrecognized thrombosis in the leg, with fatal results.

Routine leg measurements, at 10 cm. levels beginning at the lower level of the external malleolus and extending as high on the thigh as possible, on admission, before operation and before getting the patients out of bed, have been inaugurated in the hope of recognizing more cases of peripheral thrombosis and thus reducing the incidence of pulmonary embolism. The results have been encouraging, and leg measurements are recommended as a routine procedure for all hospital

patients. Any diffuse increase in the size of one or both legs over the admission measurements should suggest venous thrombosis. Other causes of enlargement are mentioned in the paper. Absolute bed rest should be instituted at once in all cases of peripheral thrombosis in an effort to prevent embolism.

AUTHOR.

Johnson, Allen S.: The Antemortem Diagnosis of Pulmonary Embolism. New England J. Med. 222: 793, 1940.

A study of forty-three fatal cases, in which autopsy revealed pulmonary embolism to have been the immediate cause of death, is presented. Dyspnea, tachycardia, and cyanosis, in contrast to pallor, are early and frequent signs. No electrocardiographic studies were possible in this series. The pitfalls in clinical diagnosis of pulmonary embolism are illustrated.

SCHWARTZ.

Drinker, Cecil K., Warren, Madeleine Field, Maurer, Frank W., and McCarrell, Jane D.: The Flow, Pressure, and Composition of Cardiac Lymph. Am. J. Physiol. 130: 43, 1940.

A method for collecting the entire lymph flow from the heart is described.

Cardiac lymph flow varies directly with the vigor of the heartbeat. It increases with dilution of the blood proteins and consequent enhancement of capillary filtration.

The composition of cardiac lymph is described in some detail in six dogs and is compared with that of the pericardial fluid.

The cardiac lymph is a filtrate from the blood capillaries. Normally it contains serum albumin and globulin and it clots. Furthermore, if horse serum is given intravenously, it can be detected immunologically in the lymph, and similarly gum acacia is also found in this lymph after intravenous injection.

AUTHORS.

Jensen, Julius, Wegner, Carl, Keys, Edgar H., Jr., and Smith, Hugh R.: Heart Disease and Pregnancy. Am. J. Obst. & Gynec. 39: 443, 1940.

The experience with cardiac patients from 1930 to 1938 in the Department of Obstetrics of Washington University is analyzed. Patients with hypertensive or degenerative heart disease were excluded unless they also suffered from valvular disease of the heart. This material conforms fairly well with the general experiences reported in the literature when distributed according to age, gravidity, etiology of heart disease, anatomic lesions, and cardiac function. Of the patients admitted to the St. Louis Maternity Hospital during this period, eight died from cardiac causes within six months of delivery. Only two of these had been regular patients of the prenatal clinic, and, on further analysis, it was found that among the patients properly handled and cooperating with the clinic, there were no deaths. This experience indicates that, while some cardiac patients should not become pregnant and should have pregnancies interrupted if they do become pregnant, the large majority of them can be carried successfully to term if given adequate prenatal care.

In the St. Louis Maternity Hospital heart disease takes a place among the causes of death comparable to that which it takes in the Boston Lying-in Hospital and the Charity Hospital in New Orleans.

Auricular fibrillation was rarely seen, but here, as elsewhere, it was found to be a serious complication. The functional classification of the cases was similar to

the general experience reported in the literature, and its prognostic value was well borne out. However, this analysis failed to establish a correlation between cardiac enlargement as shown by x-ray records and cardiac function. In one case, active rheumatic carditis prevented continuation of pregnancy. There was no evidence that patients with rheumatic heart disease are especially liable to eclampsia.

The treatment of these cases has been conducted along generally accepted lines, with gratifying results.

AUTHORS.

Ebert, Richard V., and Stead, Eugene A., Jr.: The Effect of the Application of Tourniquets on the Hemodynamics of the Circulation. J. Clin. Investigation 19: 561, 1940.

In five subjects (four normal and one with chronic arthritis) the basal blood volume averaged 5,580 c.c. The blood volume of the head, the trunk, and one arm averaged 4,680 c.c. Therefore, the average amount of blood in one upper and two lower extremities was 900 c.c., or approximately 16 per cent of the total blood volume.

In the same five subjects an average of 720 c.c. of blood was removed from head, trunk, and arm by placing venous tourniquets at diastolic pressure on three extremities. This represented 15 per cent of the volume of blood normally circulating in the head, trunk, and arm.

In four of seven normal subjects tested, sufficient blood was pooled in the extremities to produce symptoms of collapse, i.e., nausea, sweating, and pallor. In two hypertensive subjects the venous tourniquets produced a marked fall in arterial pressure and profound collapse.

In one hypertensive subject pooling of blood in the extremities caused the disappearance of a marked diastolic gallop. This indicated that the tourniquets were effective in lowering the pulmonary venous pressure.

When tourniquets were applied to the extremities, the plasma volume was lowered by transudation of fluid into the tissues. Thus the beneficial effect of the tourniquets persists in part for some time after release.

This investigation demonstrated that as much blood was removed from the general circulation by venous tourniquets as by the usual phlebotomy. It presents a rational basis for this method of treatment of left ventricular failure.

AUTHORS.

Kaltreider, Nolan L., and Palmer, Walter Lincoln: The Effect of Exercise on the Volume of the Blood. J. Clin. Investigation 19: 627, 1940.

Determinations of the volume of the blood were made at rest and variations in this volume were followed during and after varying grades of exercise in normal subjects and in individuals suffering with cardiac disease. Additional observations included measurements of the blood hemoglobin and viscosity, serum proteins, and venous pressure. The results of this investigation lead to the following conclusions:

In normal individuals during moderate exercise there is a prompt and definite decrease in the plasma volume, accompanied by a corresponding decrease in the blood volume, while the changes in the cell volume are variable though slight. These changes are associated with an increase in the blood hemoglobin and viscosity, the serum proteins and the venous and arterial pressures. Following

exercise the plasma volume gradually increases and twenty-five minutes after exercise the plasma volume, blood hemoglobin, and serum proteins reach the pre-exercise values.

During exhaustive exercise in normal subjects, there is a further decrease in plasma volume accompanied by a moderate increase in the cell volume. Twenty-five minutes after the cessation of exercise the plasma volume is still diminished and the blood hemoglobin and serum proteins are increased.

In patients with compensated heart disease, the changes in the blood volume during and following exercise are similar to those of normal subjects.

The increase in red blood cells and hemoglobin concentration resulting from exercise is brought about mainly by passage of protein-poor fluid from the vascular system into the interstitial spaces. It is only during severe or exhaustive exercise that new cells are added to the circulating blood.

AUTHORS.

Friedlander, Mae, Silbert, Samuel, and Bierman, William: Regulation of Circulation in the Skin and Muscles of the Lower Extremities. Am. J. M. Sc. **199**: 657, 1940.

Further evidence is presented to show that the regulation of the circulation in the skin differs from that in the muscles of the lower extremities. The circulation was influenced by lumbar paravertebral alcohol injections, by spinal anesthesia, by intravenous injections of hypertonic and physiologic sodium chloride solution, by adrenalin and by immersion of forearms in hot water and by typhoid vaccine. In each case temperature within calf muscles, skin temperatures of great toes, and rectal temperature were noted concurrently. Only intravenous injection of hypertonic salt solution increased circulation in both skin and muscles as indicated by temperature rises, while adrenalin injected intravenously caused a rise of muscle temperature and an initial fall of skin temperature followed by a rise. All others caused a fall in muscle temperature and a rise of skin temperature.

SCHWARTZ.

Moon, Virgil H.: Circulatory Failure of Capillary Origin. J. A. M. A. **114**: 1312, 1940.

A review is presented of the present views of peripheral circulatory failure, or circulatory failure of capillary origin. Since one of the earliest dependable signs of this condition is hemoconcentration, efforts to combat this type of circulatory deficiency must be directed toward restoration of blood volume and toward relieving the anoxia, because there is at present no means of combatting capillary atony.

SCHWARTZ.

Foote, Stephen A., Jr., Reed, Wilford C., Comeau, Wilfred J., and White, Paul D.: The Clinical Significance of Bilateral Edema of the Lower Extremities. Am. J. M. Sc. **199**: 512, 1940.

Because of the frequency with which edema of the lower extremities is attributed to congestive heart failure, and the resultant inaccurate therapy, the authors have surveyed 100 unselected cases of bilateral edema of the lower extremities from the outpatient department, and 100 cases from the medical and surgical wards, with a view to causation. In the outpatient group, the causative factors occurred in the following order: varicose veins (fifty-six cases),

with obesity (thirty-one cases), without obesity (twenty-five cases); obesity alone (thirteen cases); cardiac failure (thirteen cases); lymphedema (four cases); renal disease (three cases); nutritional factors (three cases); cirrhosis of the liver (two cases); and miscellaneous (six cases).

The ward group showed the following frequency: congestive heart failure (sixty cases); varicose veins or obesity alone or in combination (twelve cases); renal disease (seven cases); nutritional factors (seven cases); cirrhosis of the liver (seven cases); leucemia (two cases); myxedema (two cases); and miscellaneous factors (three cases).

Thus in ambulatory cases, cardiac failure as an etiologic factor is less common than often thought, although in ward cases, cardiac failure is by far the most common cause.

SCHWARTZ.

Ecker, Arthur D., Ayer, Wardner D., and O'Connor, Frederick J.: Increased Intracranial Pressure Attributed to Venous Obstruction: Beneficial Effect of Upright Posture. J. A. M. A. 114: 1440, 1940.

A case of intracranial hypertension following mastoidectomy with opening and packing of a lateral sinus is presented. It is suggested that the otitic hydrocephalus, or serous meningitis, as it is sometimes called, may be a matter of obstruction to venous outflow from the cranial cavity. In this case, maintenance of the patient's head higher than the rest of the body was followed by prompt relief of symptoms and decrease in spinal fluid pressure as well as by early subsidence of choked disks.

SCHWARTZ.

Werley, G.: Growing Interest in Heart Disease in the Southwest (Since 1915). Southwestern Med. 24: 61, 1940.

The author describes the progress made in cardiology in this region since 1915. He describes particularly the introduction of the electrocardiograph and of the interest in coronary thrombosis. He also describes the development of the Cardiac Clinic in El Paso. Changing ideas are expressed in a review of the author's personal experiences with his patients.

MCCULLOCH.

Ochsner, Alton, and Smith, M. C.: The Use of Vitamin B_1 for the Relief of Pain in Varicose Ulcers. J. A. M. A. 14: 947, 1940.

Vitamin B_1, one milligram a day in the form of Betaxin, was administered to ten patients with painful varicose ulcers. Eight showed complete subsidence of symptoms in three to eleven days. There was definite improvement in the healing of the ulcers. An explanation for the relief of pain following therapy is advanced.

SCHWARTZ.

Dean, G. O., and Dulin, J. W.: Pulmonary Embolism Following the Injection Treatment of Varicose Veins. J. A. M. A. 114: 1344, 1940.

In a series of 600 cases of varicose veins, two deaths resulted from embolism after injection therapy. In neither of these cases was there a preceding saphenous ligation, nor were the patients kept ambulatory following the injections, precautions which the authors consider necessary for best results.

SCHWARTZ.

Cogswell, H. D., and Shirley, Claxton: Treatment of Varicose Veins. Am. J. Surg. [illegible], 1939.

[illegible]

[illegible]

Smithwick, Reginald H.: The Rationale and Technic of Sympathectomy for the Relief of Vascular Spasm of the Extremities. New England J. Med. [illegible], 1940.

[illegible]

[illegible]

Cogswell, H. D., and Thomas, C. A.: Treatment of Traumatic Thrombosis of the Brachial Artery by Intermittent Venous Occlusion. J. A. M. A. 114: [illegible], 1940.

[illegible]

[illegible]

Perlow, Samuel: Prostigmine in the Treatment of Peripheral Circulatory Disturbances. J. A. M. A. 114: [illegible], 1940.

[illegible]

[illegible]

[illegible]

Grollman, Arthur, Harrison, T. R., and Williams, J. R., Jr.: Therapeutics of Experimental Hypertension. J. Pharmacol. and Exper. Therap. 69: 76, 1940.

The effect of sodium nitrate, potassium thiocyanate, erythrol tetranitrate, Allium sativum, acetyl-β-methylcholine, and renal extract on the blood pressure of rats rendered hypertensive by operative means was investigated. Only renal extract reduced the blood pressure to normal levels, all the other so-called "hypotensive" substances being inactive in this respect. The administration of relatively large amounts of sodium chloride did not markedly elevate the blood pressure.

SCHWARTZ.

Book Reviews

THE ELECTROCARDIOGRAM IN CONGENITAL CARDIAC DISEASE. By Maurice A. Schnitker, B.Sc., M.D., Formerly Resident Physician, Peter Bent Brigham Hospital and Assistant in Medicine, Harvard University Medical School. Associate Attending Physician, Toledo Hospital, etc. Harvard University Press, Cambridge, Massachusetts, 1940, 140 pages, profusely illustrated, $3.00.

The electrocardiograms in 109 cases of congenital heart disease were collected; in 106 of these cases necropsy had been performed. The material was obtained from the literature since 1915, and from various sources in Boston. Short summaries of clinical and necropsy observations are included. The cases were classified according to the method of Maude Abbott.

The author has displayed commendable energy in making this collection and attempting to analyze his material. The book will prove convenient for those who wish to refer to groups of electrocardiograms obtained from patients who were known to have had the type of congenital heart disease under consideration. The tracings are about as heterogeneous as anyone with experience in this field would expect them to be.

The attempt to correlate electrocardiographic patterns with clinical diagnoses according to the Abbott classification did not appear to be highly successful; this outcome could have been predicted. There is one error which seems significant. The tracing published as normal for a woman, 21 years old, shows a heart rate of about 120 and a Q-T interval long enough to make one suspect that the calcium content of the blood was low. Any experienced worker would need no more than one glance at such a tracing to realize that it was abnormal.

CHARLES C. WOLFERTH.

CYCLOPROPANE ANESTHESIA. By Benjamin Howard Robbins, M.D., Associate Professor of Pharmacology, Vanderbilt University School of Medicine, Williams and Wilkins, Baltimore, 1940, 175 pages, 40 illustrations, $3.00.

Dr. Robbins has been in close touch with the rapid advances in our knowledge of the use of cyclopropane as an anesthetic agent, and his own investigations of its pharmacologic properties merit careful consideration. This review of his book will be confined to the section which deals with the cardiovascular system.

The author's studies of the effect of cyclopropane on the circulatory system have led him to believe that the cardiac irregularities which occur under cyclopropane anesthesia are the result of (1) anoxemia caused by respiratory depression or arrest during deep anesthesia, or (2) of increased vagal tone secondary to premedication with morphine. In dogs which had not been premedicated, no such irregularities appeared until respiratory arrest, with a pronounced reduction in arterial oxygen saturation, had developed. With adequate artificial respiration, the concentration of cyclopropane could then be increased by about 30 per cent before the irregularities reappeared. The fact that these irregularities occurred only when the arterial oxygen saturation became reduced led him to conclude that, in the animal which had not been premedicated, they were the result of anoxemia.

Experiments on dogs which had been premedicated with morphine showed that cardiac irregularities occurred early, before cessation of respiration, when the arterial oxygen saturation was still adequate. He attributed this to the increase in vagal tone produced by morphine.

He thinks that scopolamine or atropine, which are commonly used with morphine premedication, may also predispose to cardiac irregularities, for, in therapeutic doses, they do not paralyze the vagal endings, but tend to increase the tone of the vagus center. As a substitute for morphine-scopolamine premedication, he suggests barbiturates, particularly amytal. He found that the incidence and time of onset of cardiac irregularities in dogs which had been premedicated with barbiturates were the same as in nonpremedicated animals. He agrees with Meek, Hathaway, and Orth that cyclopropane causes increased irritability of the specialized tissues of the heart, and has confirmed the observation of Waters that it increases the heart rate in dogs which have not been premedicated. He has found that, with morphine premedication, cyclopropane decreases the heart rate, whereas, with barbiturate premedication, an increase occurs.

When cyclopropane is used, the cardiac output is increased during light anesthesia, and decreased during deep anesthesia; the blood pressure rises in dogs which have not been premedicated, falls in morphinized dogs, and remains unchanged in dogs which have been premedicated with barbiturates. The effects on man are not exactly the same as on dogs.

Dr. Robbins will probably be criticized for advocating the use of barbiturates for clinical preanesthetic medication because they seem to aggravate the laryngospasm and bronchiolar constriction which sometimes occur during cyclopropane anesthesia. In addition, the barbiturates do not reduce reflex irritability or relieve pain, both of which should be accomplished by preanesthetic medication.

The book is concerned primarily with laboratory investigation. It is well organized, well written, complete, and authoritative.

STUART C. CULLEN.

Books Received

EL CORAZÓN Y LA CIRCULACIÓN EN LOS HIPERTIROIDEOS: By Dr. Héctor Gotta, Hospital Nacional de Clínicas, Buenos Aires. El Ateneo, Buenos Aires, 1938, 100 pages.

DE RÖNTGENOLOGISCHE DIAGNOSTIEK DER SCLEROSE VAN HART EN AORTA: By Dr. H. A. Snellen. 158 pages, 93 illustrations, 1939, Leiden, A. W. Sijthoff's Uitgeversmaatschappij N.V.

TEMAS DE CARDIOLOGIA, TOMO II: By Dr. Luis González Sabathié, Professor Adjunto de la Facultad de Medicina, Rosaria, Argentina, 1939, El Ateneo, 293 pages.

LAS CARDIOPATIAS Y EL PROBLEMA MEDICO-SOCIAL: By Dr. Luis González Sabathié, 1939, El Ateneo, 373 pages.

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

*Executive Committee.

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Original Communications

THE CHARACTERISTICS OF THE CHEST LEAD ELECTROCARDIOGRAMS OF 100 NORMAL ADULTS

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ROCHESTER, MINN.

IN 1932, Wolferth and Wood[1] introduced into clinical electrocardiography a precordial lead which rapidly proved to be of extreme value in many pathologic conditions.

Within the limits of variability, the various components of the Wolferth[2, 3, 4] precordial lead have been delineated gradually. As time has passed, the depth of the so-called Q wave that can be considered normal has become less, until now a so-called Q wave whose depth is not less than 2 mm. is considered normal; if it is 1 mm., or less, it is considered definitely abnormal, and, if it is less than 1.4 mm., it is considered as probably abnormal. Notching, slurring, and M or W conformations of the QRS complexes are seen in normal electrocardiograms. The take-off of the RS-T segment may range normally from 0.5 mm. above to 2.0 mm. below the isoelectric line. In normal subjects, aged 15 years or less, the T wave may be upright, but if it is upright in tracings from patients who are more than 15 years of age, it is considered abnormal.[5, 6] T waves more than 9 mm. in depth are seen in the electrocardiograms of normal persons, and therefore are not definitely abnormal.

Concomitantly with this progress, however, confusion has arisen regarding terminology and methods of obtaining the precordial lead electrocardiogram. There are two reasons for this: First, too much latitude has been allowed in methods of application; second, from the standpoint of electrical polarity, Wolferth's lead is literally "upside down" when compared to the standard leads. This is because Wolferth's original method of taking the precordial lead normally results in an inverted T wave. By Wolferth's method, relative positivity of the precordial electrode, that is, a positive electrical potential within the

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heart, is always represented in the finished tracing by a downward deflection. In a Wolferth precordial lead, the *right arm* lead wire is attached to the precordial electrode and the left arm or left leg lead wire to the indifferent electrode. In the electrocardiogram so derived, all waves directed downward (for example, the so-called Q wave and the normal T waves) represent relative positivity of the precordial electrode; all waves directed upward (for example, the so-called R wave) represent relative negativity of the precordial electrode.

In the standard, or classical, leads, this arrangement distinctly does not obtain. In Leads I, II, and III, all waves directed downward (for example, the Q and S waves) represent negative electrical potentials within the heart; all waves directed upward (for example, the R and T waves) represent positive electrical potentials in the heart.

Considered in terms of relative positivity or negativity of the precordial electrode, it is apparent that the so-called Q and R waves of *Wolferth's precordial lead are in reality R and S waves, respectively*, in the proper electrical sense in which we consider these waves in the standard leads. It was inevitable that confusion in terminology should arise under such conditions.

In an attempt to clarify the situation, the American Heart Association[7, 8] recently formulated and published a standard procedure which specifically designates the size of the precordial electrode (not to exceed 3 cm. in diameter), its exact location on the thorax, the position of the indifferent electrode, and a method of application of the lead wire that results in fourth lead waves which are exactly comparable to those of the classical leads. Adherence to the recommendation eliminates the previous source of confusion, for, in these new precordial leads, just as in the standard leads, all upward deflections represent relative positivity of the precordial electrode, and all downward deflections represent relative negativity of the precordial electrode.

Thus, in discussing the standard and new fourth leads, the terms Q, R, S, and T can be used in their correct electrical sense; that is, normally, all Q and S waves are directed downward and all R and T waves are directed upward. Because of its obvious advantages, the immediate and universal acceptance of this standard method of obtaining electrocardiograms is to be most heartily recommended. Realizing that inevitable technical difficulties might discourage the rapid acceptance of this forward step, and believing that normal standards were necessary, the following study was undertaken in October, 1937.

METHOD OF STUDY

A detailed description of the recommendations of the American Heart Association would be too voluminous to include here. For a clear comprehension of the subject matter to follow, however, some consideration of the technique employed is essential.

Precordial Electrode.—The recommendation states that the diameter of the precordial electrode is not to exceed 3 cm. A precordial electrode that complied with this specification was used in this study.

Location of the Precordial Electrode.—The recommendation designates six specific locations on the thoracic wall at which the standard electrode is to be placed. Each position is indicated by a subscript; subscript 1 denotes position 1, and so forth. For a detailed description of these positions, the reader is referred to the American Heart Association report.[7] Fig. 1 illustrates these six positions, and the following quotation from the supplementary report of the American Heart Associations[8] describes their location.

"The position of the precordial electrode shall be indicated by the subscript used, according to the following plan: subscript 1 shall be used for the right margin of the sternum; 2, for the left margin of the sternum; 3, for a line midway between the left margin of the sternum and the left midclavicular line; 4, for the left midclavicular line; 5, for the left anterior axillary line; and 6, for the left midaxillary line. When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the fourth intercostal space, and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the fourth intercostal space to the outer border of the apex beat (or to a point at the junction of the midclavicular line and the fifth intercostal space), and continued around the left side of the chest at the level of the apex beat or of the junction mentioned."

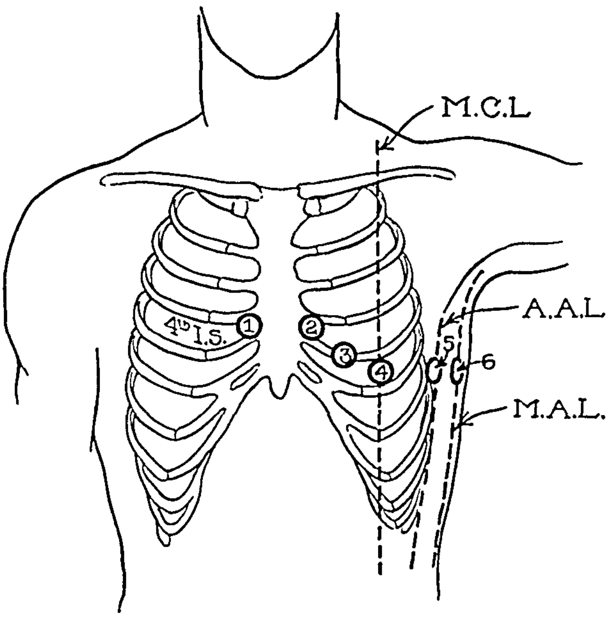


Fig. 1.—Proper points of application of the thoracic electrode to obtain the various CR, CL, and CF thoracic leads. *M.C.L.* denotes midclavicular line; *A.A.L.*, anterior axillary line; *M.A.L.*, midaxillary line; 4th *I.S.*, fourth intercostal space.

Nomenclature.—To make the specificity complete, the recommendation creates a new system for the designation of leads, which is outlined in detail. Briefly, the letters used to indicate the various leads specifically determine the position of the indifferent electrode. The letters R, L, F, and B indicate that the indifferent electrode is on the right arm (R), left arm (L), left leg (F, for foot), or back (B) (left paravertebral region), respectively. The letter C indicates that the standard electrode is placed on the thorax in one of the six positions.

Whenever the roman numeral IV is used, it means that the precordial electrode has been placed just at the outer border of the apex beat. The letter T is used

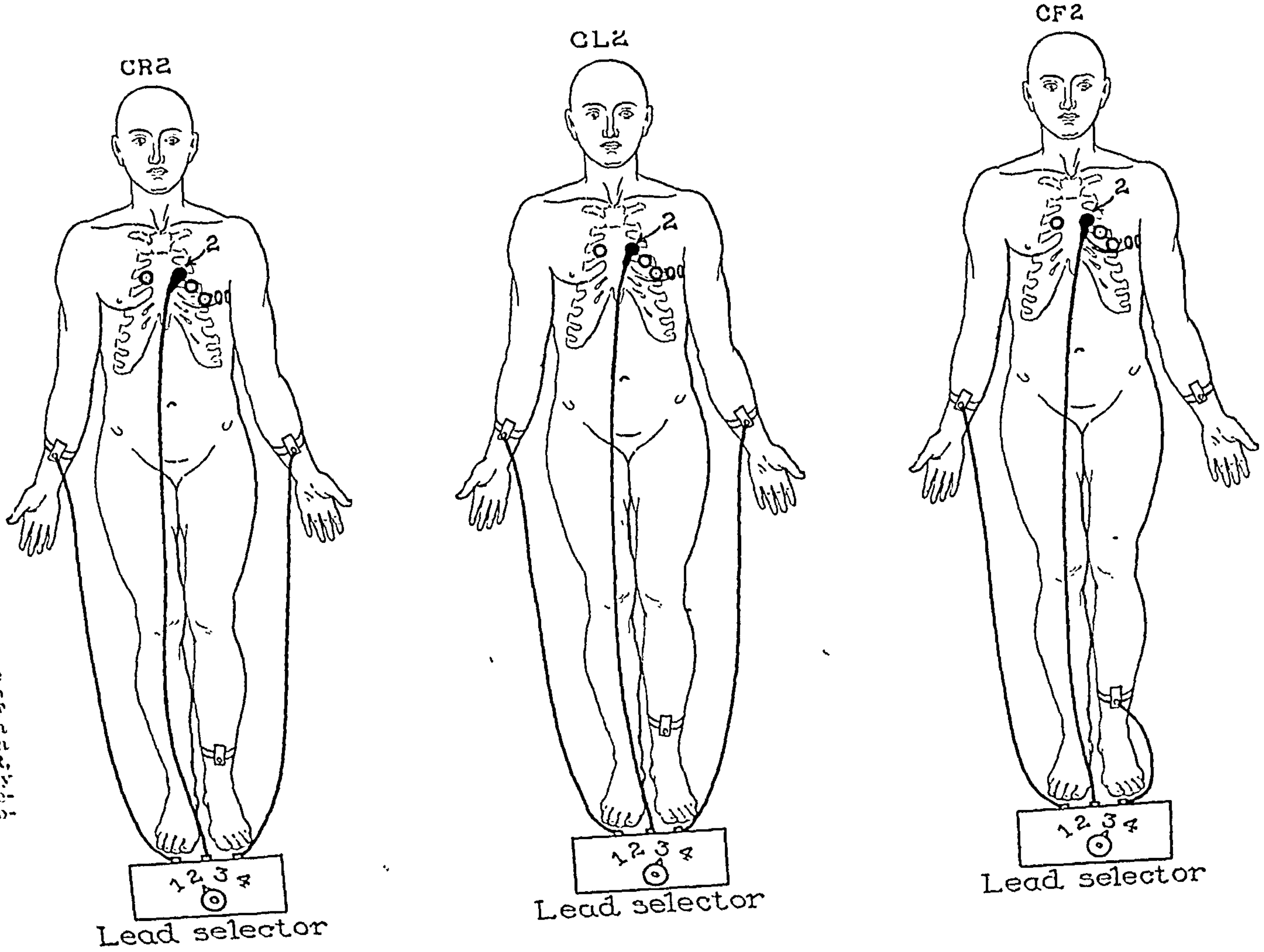


Fig. 2.—Connections of the lead wires with the oscillograph, and the lead selectors which were used in taking leads CR_2, CL_2, and CF_2. The right arm lead wire remains connected to the right arm electrode, and the left leg lead wire remains connected to the precordial electrode until all of the derivations from all six chest positions have been obtained. The left arm lead wire remains connected to the left arm electrode while CL leads are derived, and is then shifted to the left leg electrode when the CF leads are taken. Note that the precordial electrode is not touched until all leads (CR, CL, and CF) have been taken for that particular chest position. It is important that this precaution be observed if one wishes to compare CR, CL, and CF leads quantitatively for a given thoracic position. By a repetition of this method, CR, CL, and CF leads for any thoracic position of the precordial electrode may be obtained rapidly.

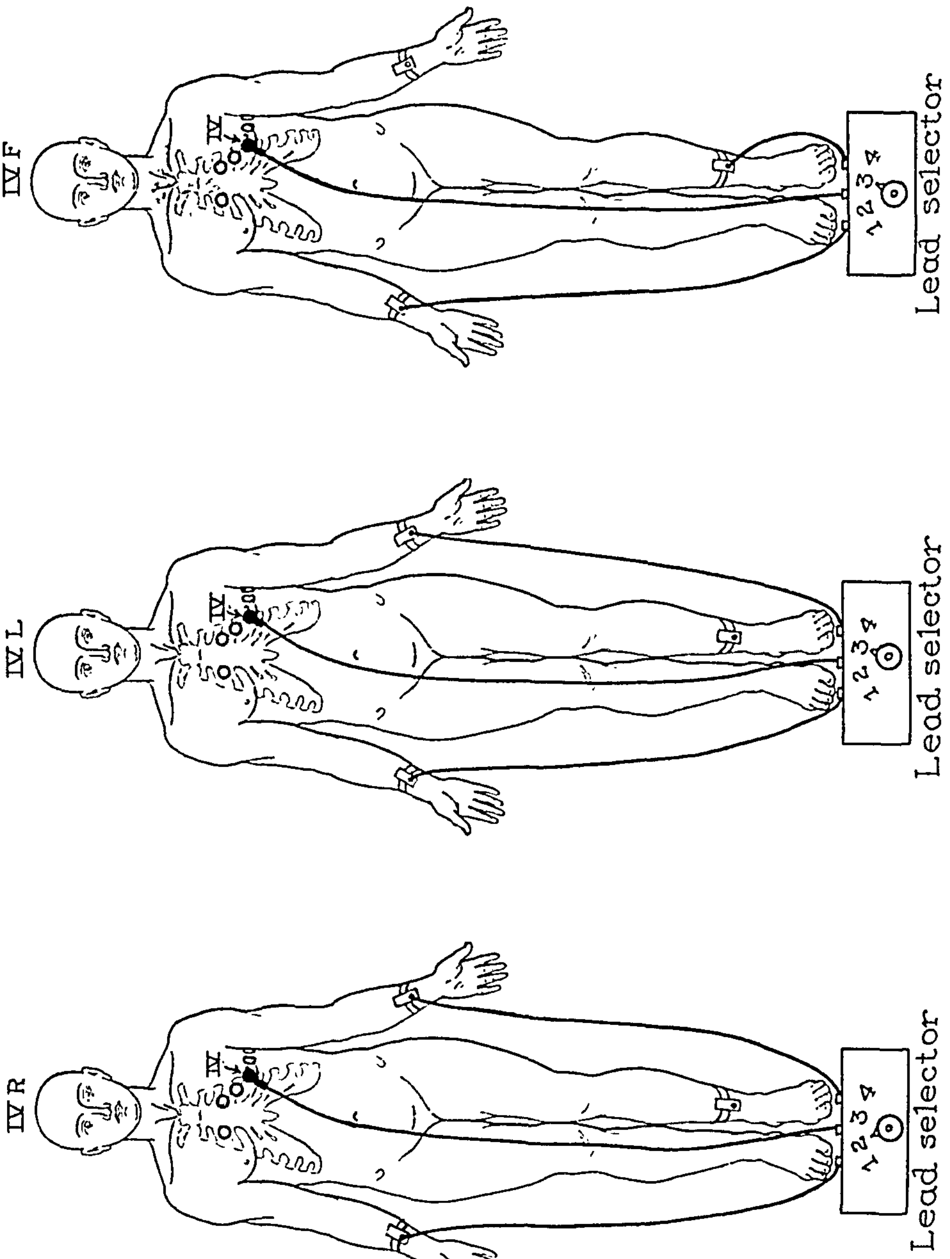


Fig. 3.—Connections of the lead wires with the oscillograph, and the lead selectors which were used in taking Leads IVR, IVL, and IVF. The position marked IV is at a point just outside the cardiac apex.

when the precordial electrode has been paired with a central terminal, connected, through equal resistances of 5,000 ohms, or more, to electrodes on each of the three extremities.

Once the reader is familiar with the new terminology, he can glance at the designation of any given lead and know exactly where the precordial electrode was, and on which part of the body the indifferent electrode was placed.

Let us consider a few examples. The designations CR_2, CL_2, and CF_2 all indicate that the precordial electrode was at position 2 (that is, in the fourth left intercostal space at the left margin of the sternum), and that the indifferent electrode was placed on the right arm (R), the left arm (L), and the left leg (F, for foot), respectively (Fig. 2). The terms CR_5, CL_5, and CF_5 indicate the respective sites of the indifferent electrodes and that the precordial electrode is now at position 5 (anterior axillary line). When the letters IVR, IVL, and IVF are used, it is immediately apparent that the precordial electrode is at the outer border of the apex beat (IV), and that the indifferent electrode is on the right arm, left arm, and left leg, respectively (Fig. 3).

Another quotation from the committee's recommendation is in order: "It will be noted that Leads CF_4 and IVF (or Lead CR_4 and Lead IVR) may sometimes be identical. In the case of the latter (Lead IVF or Lead IVR), however, the precordial electrode is placed at the outer border of the cardiac apex regardless of the position of the apex with reference to the bony landmarks of the chest, whereas, in the case of the former (Lead CF_4 or Lead CR_4), this electrode is placed in the midclavicular line even when the cardiac apex is far to the left of this position."

TECHNIQUE

All electrocardiograms were recorded by Victor Model A (oscillograph type) electrocardiographs. Frequent standardizations were performed to maintain a constant deflection of 1 cm. per millivolt. A suitable electrode paste was used to insure good contact with the skin. This was found to be of vital importance in obtaining a satisfactory and uniform contact for the precordial electrode.

At all times, the derivations used in this study were obtained in such a manner as to conform exactly to the recommendations of the American Heart Association.[7, 8] The precordial electrode which was used measured exactly 3 cm. in diameter. The new nomenclature was employed throughout, and at all times the technique was so arranged that, except for the Wolferth leads, the presence of a relatively positive electrical potential at the precordial electrode was represented in the finished tracing by an upward deflection.

MATERIAL FOR STUDY

A preliminary study was made on ten apparently healthy and normal adults (six men and four women) who ranged in age from 21 to 33 years, with an average age of 26.9 years. Only those whose history was free from even a suggestion of cardiac disease or an attack of rheumatic fever, who had normal blood pressure and a heart of normal size and configuration, as ascertained by stereoscopic roentgenograms of the thorax, were considered normal. The standard Leads I, II, and III were taken in the usual fashion.

In taking the multiple precordial leads, a long, perforated, elastic thoracic band was used. It was fastened in place by means of hooks on the flat, rectangular electrode which was an integral part of the band. This band was fitted snugly about the thorax in such a way that posteriorly the attached electrode was in contact with the skin of the back just to the left of the spine at about the level of the angle of the scapula; anteriorly the six precordial positions were covered by the elastic strap. The posterior electrode was used as the indifferent electrode

in obtaining Lead IVB and the Wolferth leads. Anteriorly, the band held the 3-centimeter electrode firmly in place at any desired location.

The skin at position 1 was prepared by rubbing a suitable electrode paste into the skin where the electrode was to be placed. The importance of a suitable, conductive electrode paste cannot be minimized. Comparing Fig. 4*A* (no paste) with Fig. 4*B* (with paste), we see easily the marked change that results when good contact is achieved by means of paste. The amplitude is markedly increased, and, in other instances, the "abnormal" S-T segment which was obtained when paste was not used was even more striking than that shown in Fig. 4*A*. A comparison of Lead CR_1 when taken from dry skin, rubbed with plain water, and skin rubbed with electrode paste is shown in Fig. 4*B* (CR_1 dry; CR_1 wet; CR_1 with paste).

After the skin had been prepared, the precordial electrode was placed at position 1, and, without disturbing the lead wires of the right and left arms, the lead wire from the left leg was disconnected from its electrode and attached to the precordial electrode.

With the lead selector on Lead II (right arm lead wire to left leg lead wire), Lead CR_1 was obtained. Simply by switching the lead selector to Lead III (left arm lead wire to left leg lead wire), Lead CL_1 was recorded.

With the lead selector still on Lead III, and without disturbing anything else, the single maneuver of disconnecting the left arm lead wire from the left arm electrode and reconnecting it to the left leg electrode produced Lead CF_1.

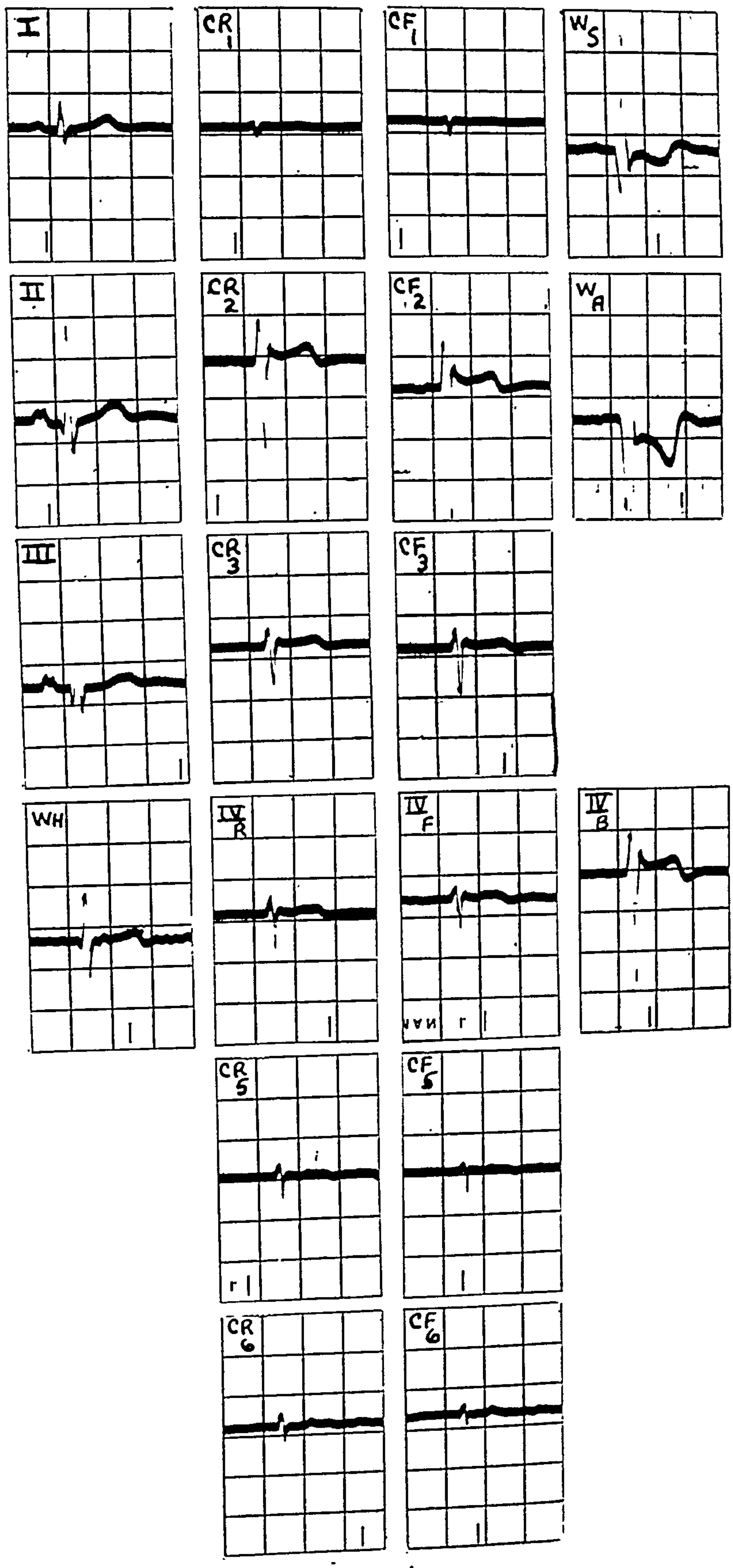
Thus, Leads CR_1, CL_1, and CF_1 were derived with a minimum of effort. As soon as CF_1 was completed, the left arm lead wire was returned to its normal position on the left arm. The precordial electrode, with the left leg lead wire attached, was moved to the freshly prepared position 2. With the lead selector first on Lead II, and then on Lead III, Leads CR_2 and CL_2, respectively, were rapidly obtained. With the lead selector still on Lead III, the left arm lead wire was again shifted to the left leg electrode, and Lead CF_2 was obtained, following which the left arm lead wire was returned to its normal position to be ready for the next series of three derivations.

Utilizing this system, CR, CL, and CF leads, at positions 1 to 6, inclusive, were rapidly obtained as the precordial electrode was shifted from one to another of the six thoracic locations. As soon as all six CR, CL, and CF leads were finished, the limb electrodes were permanently removed.

The Whitten lead was taken next. The right arm electrode, with the corresponding lead wire attached, was placed in the right axilla on a level with the heart. Similarly, the left arm electrode, attached to its lead wire, was placed in the left axilla. By this means, with the lead selector on Lead I, the Whitten lead,[9] or an amplified Lead I, is obtained.

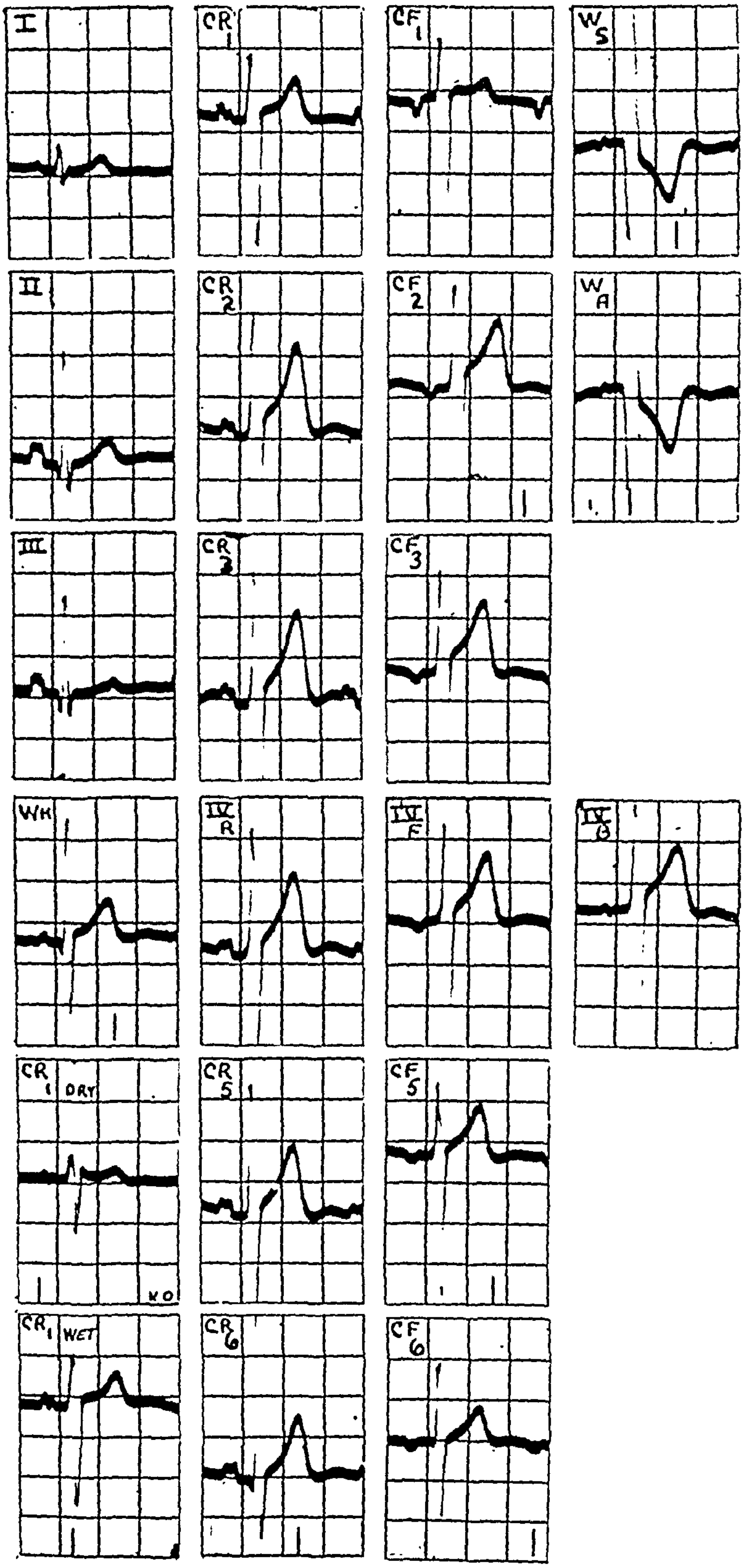
Next, the Wolferth precordial anteroposterior thoracic leads were obtained. Two such thoracic leads were taken to permit comparison with the changes which occurred when the precordial electrode was shifted from position 2 to a location just outside the apex beat. The right arm lead wire was connected to the precordial electrode which was formerly used in the laboratory (8 cm. in diameter), and this electrode was placed with its center at position 3. The left arm wire was connected to the indifferent electrode previously described, which was situated to the left of the vertebral column at about the level of the angle of the scapula. This arrangement resulted in what was designated "Wolferth standard," as this had been the "standard" type of Wolferth lead previously in use in the laboratory.

To compare the relative effect, if any, of using this large electrode, the standard 3-centimeter precordial electrode was then placed at position 2, with the right arm lead wire attached to it, and the lead designated as "Wolferth" (small electrode at position 2) was obtained.



A.

Fig. 4.—Electrocardiogram of a normal man. Thoracic lead electrocardiograms obtained (*A*) without and (*B*) with the use of an electrode paste. Note that, by using the paste, not only is there an increase in the amplitude of the deflections, but also that certain S-T segment contours that appear abnormal in the tracings obtained without the use of the paste have disappeared. The nomenclature of lead designations is explained in the text.


I
CR 1
CF 1
W S
II
CR 2
CF 2
W A
III
CR 3
CF 3
WH
IV R
IV F
IV B
CR 1 DRY
CR 5
CF 5
CR1 WET
CR 6
CF 6

B.

The lead designated as "Wolferth apex" was derived by moving the small precordial electrode with its attached right arm lead wire from position 2 to the outer border of the apex beat, so that it occupied exactly the same position as it did when Leads IVR, IVL, and IVF were taken.

Finally, by leaving the electrodes in the position they occupied for taking the Wolferth apex lead, and by simply reversing the attachments of the right and left arm lead wires, so that the right arm wire was now connected to the posterior electrode and the left arm wire to the apical electrode, Lead IVB was obtained.

Thus, on each of these ten normal subjects the following leads were available for study: I; II; III; CR_1, CL_1, CF_1; CR_2, CL_2, CF_2; CR_3, CL_3, CF_3; IVR, IVL, IVF (the electrode was always placed at the outer border of the apex, so that IVR, IVL, and IVF, rather than CR_4, CL_4, and CF_4, would be obtained); CR_5, CL_5, CF_5; CR_6, CL_6, CF_6; Whitten (WH); Wolferth Standard (WS); Wolferth (small electrode at position 2); Wolferth apex (WA); and IVB.

Figs. 5 and 6 illustrate typical series on a man and a woman, respectively. The Wolferth lead (small electrode at position 2) was not included in the illustration, for this lead was taken merely to ascertain whether the use of the 3-centimeter electrode resulted in exactly the same tracing as that which was obtained when the large, old-style electrode was used. By actual comparison, it soon became apparent that the small electrode did *not* affect the tracings obtained from normal subjects.

The P, Q, R, S, and T waves, and the relation of the take-off of the S-T segment to both the P-R and T-P base lines of each of these derivations in the tracings from each subject in this group, were accurately measured, recorded, and tabulated as to maximal, minimal, and average amplitude. The average P-R and QRS intervals were recorded for each lead, also. The average values for the various leads are shown in Table I.

In the recommendation, the committee stated: "It is suggested for all ordinary purposes that Lead IVR or Lead IVF be employed. The latter lead should have preference until it has been established that the former, which is somewhat more convenient, is equivalent to the latter for all practical purposes, or yields results of equal value."

From Table I it is evident that, quantitatively, the CR, CL, and CF leads are *not* interchangeable. It is apparent that the CR leads give the greatest amplitude, and CF leads, the least. The P waves were usually comparable to those of the standard leads when Leads CR and CL were used, but usually were inverted or diphasic in CF leads.

As these conclusions were based on such a small series, a more comprehensive study on 100 normal adults was undertaken. Because of the time, technical aid, and large quantity of film required, it seemed advisable to compare only two, instead of all three, CR, CL, and CF leads. The recommendation just quoted, and the convenience and seeming anatomic soundness of the CR leads as compared to the CL leads, plus the other aforementioned factors, led to selection of the CR and CF leads for comparison in the larger series. This series comprised fifty men and fifty women, all of whom met the requirements laid down for the preliminary survey on the ten normal adults.

TABLE I

SUMMARY OF THE STUDY OF THE STANDARD ELECTROCARDIOGRAMS AND PRECORDIAL LEADS ON TEN NORMAL ADULTS (THIS SERIES INCLUDES CL LEADS)*

LEAD	P WAVE		Q WAVE		R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT				P-R INTERVAL, AVERAGE DURATION, MM.	AVERAGE DURATION OF QRS, MM.
											FROM P-R		FROM T-P			
	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.		
I	+10	+0.4	− 3 0= 7	−0.4	+10	+ 6.2	− 9 0= 1	− 1.1	+10	+2.0	+ 6 0= 4	+0.2	0=10	0	0.14	0.07
II	+10	+0.9	− 4 0= 6	−0.5	+10	+12.9	− 7 0= 3	− 1.9	+10	+2.4	+ 4 − 2 0= 4	+0.9 −0.5	+ 2 − 6 0= 2	+0.3 −0.3	0.15	0.07
III	+10	+0.5	− 5 0= 5	−0.6	+10	+ 6.3	− 6 0= 4	− 1.2	− 7 − 1 di 2	+0.8 −0.8	+ 3 − 1 0= 6	+0.3 −0.2	+ 6 − 5 0= 4	+0.3 −0.2	0.15	0.08
CR_1	+10	+0.9	0=10	0.0	+10	+ 4.4	−10	− 9.7	+ 9 so 1	+3.0	+10	+0.9	+ 8 0= 2	+0.6	0.15	0.08
CR_2	+10	+1.0	0=10	0.0	+10	+ 8.4	−10	−16.9	+10	+9.3	+10	+1.9	+ 9 0= 1	+1.7	0.15	0.08
CR_3#	+9	+0.9	0= 9	0.0	+ 9	+10.5	− 9	−14.3	+ 9	+9.8	+ 9	+1.9	+ 9	+1.6	0.15	0.08
IVR	+10	+1.0	0=10	0.0	+10	+15.5	−10	−11.7	+10	+9.0	+ 9 0= 1	+1.6	+ 9 − 1	+1.2 −1.0	0.15	0.08
CR_5	+10	+1.0	− 4 0= 6	−0.6	+10	+27.4	−10	−6.46	+10	+7.5	+ 8 − 2	+1.0 −0.5	+ 8 − 2	+0.8 −1.0	0.15	0.08
CR_6	+10	+0.9	− 7 0= 3	−0.8	+10	+24.1	− 9 0= 1	− 2.1	+10	+4.7	+ 6 − 1 0= 3	+0.5 −0.3	+ 5 − 2 0= 3	+0.3 −0.6	0.14	0.08

TABLE I—CONT'D

LEAD	P WAVE		Q WAVE		R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT				P-R INTERVAL, AVERAGE DURATION, MM.	AVERAGE DURATION OF QRS, MM.
											FROM P-R		FROM T-P			
	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.		
CL$_1$	+5 di 5	+0.6	0=10	0.0	+10	+ 3.3	−10	−12.8	+ 4 − 3 di 3	+2.0 −0.8	+ 9 0= 1	+0.9	+ 9 0= 1	+0.7	0.14	0.08
CL$_2$	+10	+0.5	0=10	0.0	+10	+ 7.2	−10	−17.9	+10	+6.3	+10	+1.9	+10	+1.5	0.14	0.08
CL$_3$#	+9	+0.5	0= 9	0.0	+ 9	+ 7.4	− 9	−14.5	+ 9	+7.4	+ 8 0= 1	+1.8	+ 9	+1.6	0.14	0.08
IVL	+10	+0.5	0=10	0.0	+10	+10.6	−10	−10.8	+10	+6.1	+ 9 0= 1	+1.3	+ 9 − 1	+1.1 −0.7	0.14	0.08
CL$_4$	+10	+0.4	− 3 0= 7	−1.1	+10	+21.2	−10	− 5.5	+10	+5.2	+ 7 − 2 0= 1	+0.7 −0.4	+ 7 − 2 0= 1	+0.7 −0.6	0.15	0.08
CL$_6$	+10	+0.4	− 6 0= 4	−0.9	+10	+18.9	− 7 0= 3	− 1.0	+10	+2.8	+ 4 − 1 0= 5	+0.5 −0.2	+ 4 − 1 0= 5	+0.3 −0.2	0.15	0.07
CF$_1$	+2 −4 di 4	+0.8 −0.9	0=10	0.0	+10	+ 2.6	−10	−18.3	+ 4 − 6	+1.9 −1.0	+ 9 0= 1	+0.9	+ 9 0= 1	+0.9	0.14	0.08
CF$_2$	+2 −4 di 4	+0.7 −0.5	0=10	0.0	+10	+ 6.4	−10	−23.7	+10	+6.0	+10	+1.9	+10	+1.9	0.13	0.08
CF$_3$#	+2 −2 di 5	+0.3 −0.4	− 1 0= 8	−0.1	+ 9	+ 6.9	− 9	−16.5	+ 9	+6.7	+ 9	+1.8	+ 9	+1.8	0.14	0.08

IVF	+4 -2 di 4	+0.3 -0.3	- 1 0= 9	-1.2	+10	+ 7.5	-10	-13.1	+10	+5.9	+10	+1.9	+10	+1.9	0.13	0.08
CF_5	+4 -2 di 4	+0.5 -0.3	- 4 0= 6	-1.0	+10	+19.3	-10	- 7.0	+10	+4.8	+ 8 - 2	+0.7 -0.4	+ 8 - 2	+0.7 -0.4	0.14	0.07
CF_6	+2 -1 di 7	+0.4 -0.2	- 7 0= 3	-1.2	+10	+13.1	- 8 0= 2	- 2.2	+10	+2.5	+ 4 - 2 0= 4	+0.4 -0.2	+ 5 - 2 0= 3	+0.3 -0.2	0.14	0.07
Wolferth standard	-6 di 4	-0.5	0=10	0.0	-10	- 8.3	+10	+20.3	-10	-7.5	-10	-2.0	-10	-1.8	0.15	0.08
Wolferth sm. elec. #2	-6 di 4	-0.5	0=10	0.0	-10	- 8.0	+10	+19.2	-10	-7.1	-10	-2.0	-10	-1.8	0.15	0.08
Wolferth apex	-7 di 3	-0.4	+ 1 0= 9	+0.2	-10	-12.5	+10	+13.0	-10	-6.0	-10	-1.2	- 9 0= 1	-1.2	0.15	0.08
IVB	+9 poly 1	+0.4	- 1 0= 9	-0.2	+10	+13.1	-10	+12.5	+10	+6.8	+10	+1.1	+ 9 0= 1	+1.0	0.15	0.08
Whitten	+10	+0.7	- 7 0.3	-3.4	+10	+22.8	- 8 0= 2	- 1.1	+10	+4.1	+ 6 - 2 0= 2	+0.5 -0.4	+ 4 - 2 0= 4	+0.4 -0.8	0.14	0.08

*The sign "+" indicates that the deflection is directed upward from the base line.
The sign "–" indicates that the deflection is directed downward from the base line.
The letters "di" indicate that the deflection was diphasic.
The numeral "0" indicates that no deflection, for the wave designated, occurred.
The syllable "poly" denotes that the deflection was polyphasic.
The sign "∓" indicates that, because of the peculiar contour of the heart, position C_3 coincided with position 4 on the chest of one female. Hence, CR_3, CL_3 and CF_3 tracings were obtained on only nine patients of this series.
The sign "=" in such an expression as "0 = 7" means that the designated deflection was absent seven times.
The letters "iso" indicate that the deflection was isoelectric.

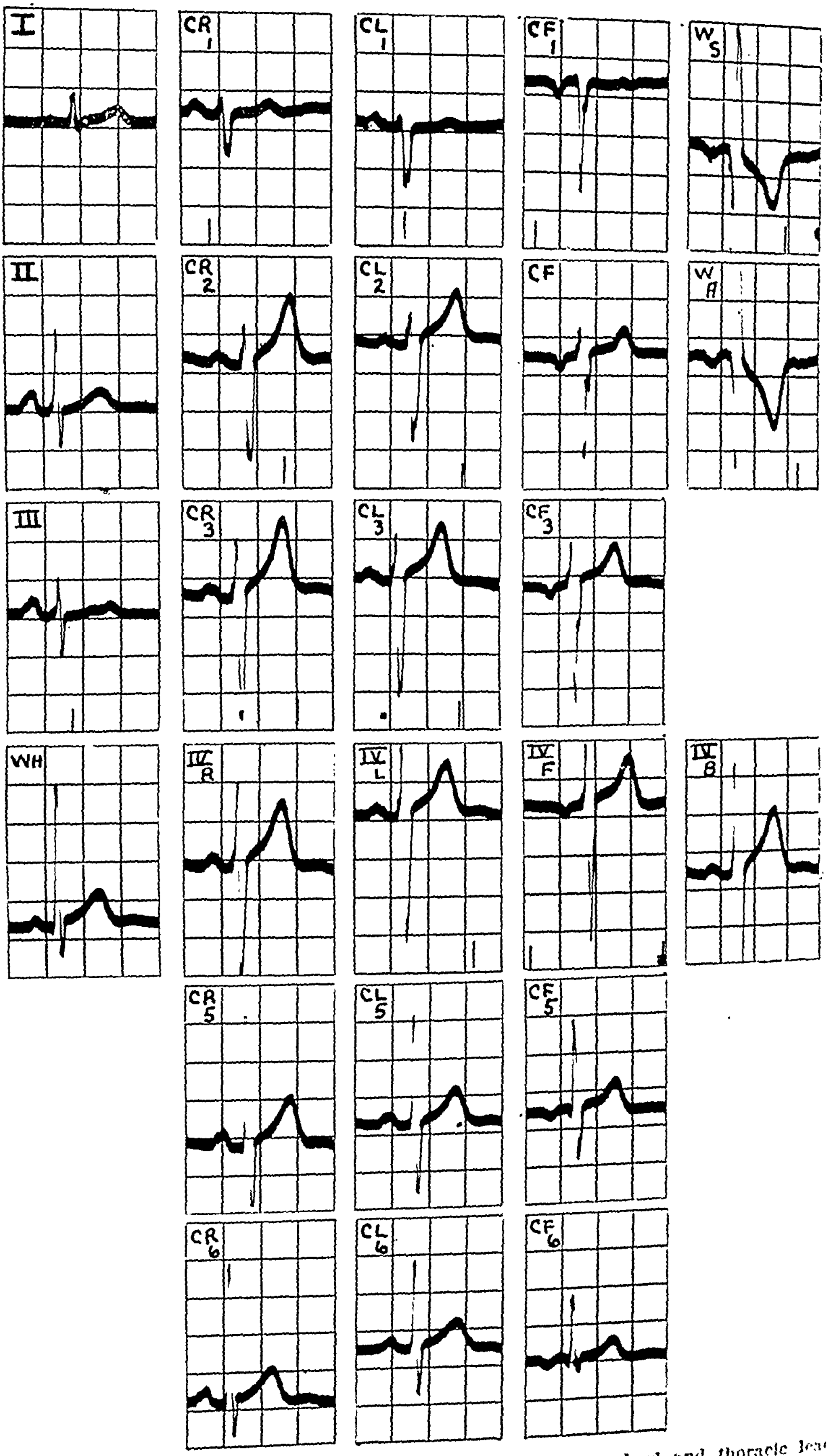


Fig. 5.—An average example of the entire series of standard and thoracic lead electrocardiograms, obtained from a normal man. At a given position, the three leads, CR, CL, and CF, were taken before the thoracic electrode was moved. Note that changing the location of the indifferent electrode results in some variation in the electrocardiograms which are obtained with any given position of the thoracic electrode.

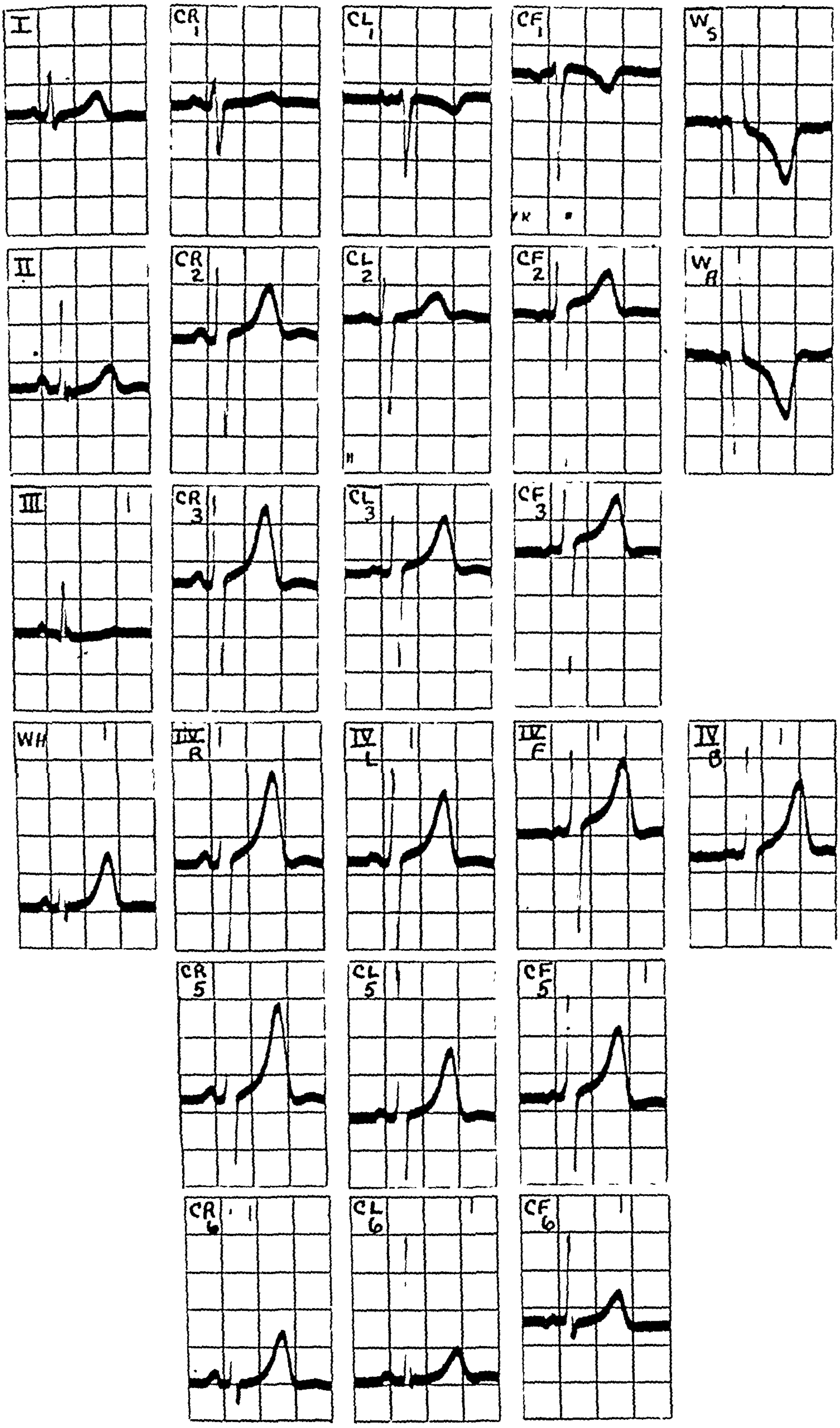


Fig. 6.—An average example of the entire series of standard and thoracic lead electrocardiograms, obtained from a normal woman.

The ages of these one hundred normal adults varied from a minimum of 17 years to a maximum of 47 years. The average age for the entire group was 28.4 years. No attempt was made to select subjects of an average habitus.

The various electrocardiograms were obtained as they were in the preliminary study, except that Wolferth leads (with the small electrode at position 2) and CL leads were not taken.

The fact that CL leads were not taken simplified the technique somewhat. As soon as the standard leads were finished, the left arm electrode was permanently disconnected. With the right arm lead wire connected to the right arm and the left arm lead wire connected to the left leg, the left leg lead wire was attached to the precordial electrode. With this arrangement of the lead wires, and with the precordial electrode at position 1, Lead CR_1 was obtained when the lead selector was placed on Lead II, and Lead CF_1 was obtained when it was placed on Lead III. Thus, Leads CR and CF, 1 to 6, were rapidly derived by the simple maneuvers of moving the precordial electrode from one position to another, and switching the lead selector to Lead II for the CR leads and to Lead III for the CF lead. As before, Leads IVR and IVF were taken in all cases in which the apex beat was palpable.

Thus, on each subject, the following leads were available for analysis: I, II, III; CR_1 and CF_1; CR_2 and CF_2; CR_3 and CF_3; IVR and IVF (the electrode was always placed at the outer border of the apex, so that IVR and IVF, rather than CR_4 and CF_4, would be obtained); CR_5 and CF_5; CR_6 and CF_6; Whitten (WH); Wolferth (Standard) (WS); Wolferth apex (WA); IVB and standardization (ST). Each lead was subjected to the same careful quantitative analysis as in the preliminary series of ten subjects, and the final measurements were recorded in tabular form.

Table II shows the direction and average amplitude of the various deflections, as well as the average conduction times in the series of fifty normal adult men. Table III is a similar summary of the observations on fifty normal adult women. Table IV summarizes the final averages for both men and women. Tables V and VI supply the maximal and minimal values of the amplitudes of the various deflections for fifty men and fifty women.*

P Wave.—As a rule, in CR and CL leads the P wave is upright. In CF leads it is usually inverted or diphasic. "Notching" of the P wave was very commonly encountered. If slight indentations are considered as "notching," this feature occurred in more than 90 per cent of the cases.

Q Wave.—A true Q wave is rare at the first three positions; it occurred only once in CR_1, once in CR_3, and once in CF_3. The farther to the left the electrode is moved, the more common and pronounced this wave becomes. The so-called Q wave of the Wolferth leads is designated as an R wave in this discussion, because that is what it really is. A true Q wave was frequently present at the fourth, fifth, and sixth positions (Fig. 7), and occasionally a true Q wave (an initial upward deflection of the QRS complex) was discernible in the Wolferth apex lead (Fig. 7).

*Because of the short distance from the apical impulse to the sternal border in one of the women, no third position could be used without marked overlapping of positions 2 and 4. In this case, therefore, CR_3, CL_3 and CF_3 leads were not obtained. Thus, all components total only 49 or 99, respectively, when third position derivations are being considered.

R Wave.—The amplitude of the R wave is greater in all of the CR leads than in the CL and CF leads. It is apparent that the R wave in CL, CF, and Wolferth leads (so-called Q wave in the latter) will exhibit a significant decrease in amplitude, or will even disappear completely, more readily than will the R wave in the CR leads. The smallest R (so-called Q) wave in the Wolferth standard lead measured 1.0 mm. (WS in Fig. 8). In this same lead and in the same individuals, R waves frequently measured 2.3 mm. (WS_1 in Fig. 8). In the Wolferth leads, the R (so-called Q) wave is usually longer at position 4 than at position 2. Occasionally, however, the reverse was observed.

S Wave.—Nothing specific can be said regarding the S wave that is not apparent from the tables. Its range of variability is tremendous.

T Wave.—At position 1 the T wave is rarely negative, but it is frequently diphasic in the CR leads; it is slightly more commonly negative or diphasic in CL leads, and is usually negative or diphasic in CF leads. At all other positions it was always upright, except at position 6, where it was rarely diphasic or polyphasic, but never actually inverted. With one exception, the T wave in all Wolferth leads was normally inverted. This exception occurred in the case of a woman in the standard Wolferth derivation. This subject's apex beat was situated at the site ordinarily reserved for position 3. Therefore, position 3 was not available. This subject was perfectly healthy, and she had passed through pregnancy and parturition without incident. All of the leads in this case were retaken, but re-examination of them failed to reveal this pathologic T wave in the Wolferth lead. It is interesting to note that, in this case, when a Wolferth anteroposterior lead was taken with the standard electrode at position 2 (fourth intercostal space) and when additional anteroposterior leads were taken with the precordial electrode in the second or third intercostal space parasternally, the T waves were all inverted (normal). However, when the electrode was placed high in the epigastric notch, over the xiphoid, the T wave was again abnormally upright. The fact that the T wave at position 2 was originally upright was *not* the result of placing the electrode too low over the heart.

In the case of one man, marked notching of the T wave in IVF occurred; this was less evident in IVB (Fig. 9). It is interesting that notching of the T wave was more marked in IVB than it was in the Wolferth apex lead, although the latter is obtained in exactly the same manner as IVB; the only difference is that the lead wires are reversed. In the standard leads in the case of one man (Fig. 10), there were a diphasic T wave in Lead I, frankly inverted T waves in Leads II and III, and a diphasic tendency in some of the T waves in the precordial leads. Another man (Fig. 11) had a diphasic T wave in Lead II and a frankly inverted, almost "cove-plane," T wave in Lead III. The nearest thing to negativity of a T wave at position 2 in the precordial leads was observed in a woman (Fig. 12, Lead CF_2).

TABLE II

SUMMARY OF THE STUDY OF THE STANDARD ELECTROCARDIOGRAMS AND PRECORDIAL LEADS ON FIFTY NORMAL MALES (CL LEADS WERE NOT STUDIED IN THIS SERIES)*

LEAD	P WAVE		Q WAVE		R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT				P-R INTERVAL, AVERAGE DURATION, MM.	AVERAGE DURATION OF QRS, MM.
											FROM P-R		FROM T-P			
	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.		
I	+50	+0.5	−17 0=33	−0.4	+50	+ 6.4	−42 0= 8	− 1.9	+49 di 1	+ 2.5	+33 − 3 0=14	+0.3 −0.1	+12 − 9 0=29	+0.3 −0.2	0.14	0.09
II	+50	+1.1	−25 0=25	−0.6	+50	+12.1	−44 0= 9	− 2.8	+47 − 1 di 2	+ 3.1 − 1.3	+44 − 6 0= 3	+0.5 −0.6	+18 −17 0=15	+0.4 −0.5	0.16	0.08
III	+44 − 3 di 3	+0.7 −0.3	−30 0=20	−0.9	+50	+ 7.1	−36 0=14	− 2.6	+35 di 8	+ 1.2 − 1.0	+32 −11 0= 7	+0.3 −0.2	+10 −20 0=20	+0.3 −0.4	0.15	0.08
CR_1	+49 − 1 di 0	+1.0 −0.3	− 1 0=49	−0.0	+49 0= 1	+ 5.0	−49 0= 1	−10.1	+47 − 1 di 2	+ 3.3 − 0.4	+50	+1.0	+42 − 1 0= 7	+0.8 −0.1	0.15	0.08
CR_2	+48 di 2	+1.1	0	0.0	+50	+10.9	−50	−19.6	+50	+ 9.8	+50	+2.1	+49 − 1	+1.7 −0.3	0.15	0.08
CR_3	+49 di 1	+1.1	− 1 0=49	−0.2	+50	+13.0	−50	−17.9	+50	+10.3	+50	+2.1	+49 0= 1	+1.8	0.15	0.08
IVR	+49 di 1	+1.1	− 5 0=45	−0.5	+50	+19.2	−50	−13.8	+50	+ 9.9	+49 0= 1	+1.7	+48 − 1 0= 1	+1.3 −0.4	0.15	0.08
CR_4	+49 iso 1	+1.2	−19 0=31	−0.7	+50	+26.4	−49 0= 1	− 8.2	+50	+ 8.3	+47 − 1 0= 2	+1.1 −0.4	+40 − 5 0= 5	+0.9 −0.3	0.15	0.08

CR₄	+49 iso 1	+1,2	−37 0=13	−1,0	+50	+11,6	−50	−4,1	+19 di 1	+5,9	+13 −4 0=3	+0,7 −0,3	+30 −9 0=11	+0,6 −0,4	0,15	0,08
CF₁	+5 −36 di 9	+0,8 −0,3	0	0,0	+51	+3,3	−51	17,0	+16 −29 di 5	+2,2 −1,9	+13 −4 0=3	+0,7 −0,2	+45 −2 0=3	+0,7 −0,1	0,14	0,08
CF₃	+13 −25 li 12	+0,4 −0,6	0	0,0	+50	+8,4	−50	−23,4	+50	+7,1	+50	+1,9	+50	+1,9	0,14	0,09
CF₂	+13 −17 li 20	+0,4 −0,5	−1 0=19	−1,4	+50	+9,2	−50	−21,1	+50	+7,3	+50	+1,8	+50	+1,8	0,14	0,08
IVF	+17 −16 di 17	+0,4 −0,4	−3 0=47	−0,8	+50	+11,8	−50	−14,5	+50	+7,0	+49 −1	+1,3 −0,2	+49 0=1	+1,4	0,14	0,08
CF₄	+19 −8 di 23	+0,4 −0,4	−16 0=34	+0,7	+50	+16,4	−50	−7,4	+50	+5,4	+40 −2 0=8	+0,7 −0,7	+44 −2 0=4	+0,7 −0,7	0,15	0,08
CF₆	+17 −13 di 20	+0,3 −0,3	−33 0=17	1,4	+50	+13,4	−37 0=13	−2,5	+48 di 2	+2,8	+21 −13 0=16	+0,4 −0,2	+31 −5 0=14	+0,3 −0,2	0,15	0,07
Wolferth standard	+48 di 2	+0,5	0,0	0	+50	+10,9	−50	−23,6	+50	+8,6	+50	+2,3	+48 0=2	+2,1	0,16	0,09
Wolferth apex	−49 di 1	−0,5	−1 0=49	+0,3	+50	−15,3	−50	+17,1	50	+8,6	+50	+1,8	+50	−1,6	0,16	0,08
IVB	+49 di 1	+0,5	−1 0=49	+0,1	+50	+15,6	−50	−16,2	+50	+8,6	+50	+1,7	+50	+1,5	0,16	0,08
Whitten	+49 di 1	−0,9	−42 0=8	−1,0	+50	+21,1	−42 0=8	−3,2	+48 −0 di 2	+5,1	+30 −13 0=7	+0,6 −0,3	+23 −17 0=10	+0,5 −0,5	0,14	0,08

*The signs have the same significance as they have in Table I.

TABLE III

SUMMARY OF THE STUDY OF THE STANDARD ELECTROCARDIOGRAMS AND PRECORDIAL LEADS ON FIFTY NORMAL ADULT FEMALES (CL LEADS WERE NOT STUDIED IN THIS SERIES)*

LEAD	P WAVE		Q WAVE		R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT				P-R INTERVAL, AVERAGE DURATION, MM.	AVERAGE DURATION OF QRS, MM.
											FROM P-R		FROM T-P			
	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.		
I	+50	+0.5	−11 0=39	−0.2	+50	+ 4.8	−39 0=11	− 1.1	+50	+1.7	+25 − 8 0=17	+0.2 −0.1	+ 5 −19 0=26	+0.0 −0.1	0.14	0.07
II	+50	+1.2	−24 0=26	−0.5	+50	+11.1	−35 0=15	− 1.9	+50	+2.2	+17 −18 0=15	+0.3 −0.3	+ 3 −35 0=12	+0.0 −0.6	0.15	0.08
III	+47 di 3	+0.7	−33 0=17	−0.8	+50	+ 7.0	−30 0=20	− 1.5	+25 − 5 di 20	+1.0 −1.0	+15 −18 0=17	+0.2 −0.2	+ 4 −34 0=12	+0.1 −0.4	0.15	0.07
CR$_1$	+49 di 1	+0.9	0.0	0.0	+48 0= 2	+ 3.2	−50	− 9.3	+43 − 0 di 7	+1.8	+47 0= 3	+0.6	+35 − 6 0= 9	+0.4 −0.3	0.15	0.08
CR$_2$	+50	+1.0	0.0	0.0	+50	+ 5.9	−50	−16.6	+50	+6.2	+50	+1.3	+45 − 2 0= 3	+0.9 −0.4	0.15	0.08
CR$_3$#	+49	+1.1	0.0	0.0	+49	+ 7.7	−49	−13.8	+49	+7.0	+49	+1.2	+43 − 4 0= 2	+0.8 −0.2	0.15	0.08
IVR	+50	+1.1	0.0	0.0	+50	+11.7	−50	−11.0	+50	+7.7	+48 − 1 0= 1	+1.1 −0.0	+43 − 5 0= 2	+0.7 −0.6	0.15	0.08
CR$_5$	+50	+1.2	− 9 0=41	−0.6	+50	+21.5	−47 0= 3	− 5.4	+50	+7.1	+41 − 5 0= 4	+0.6 −0.4	+31 −12 0= 7	+0.4 −0.5	0.15	0.08

CR_6	+49 −1	+1.2 −0.6	−25 0=25	−0.7	+50	+10.3	−34 0=16	−2.9	+50	+5.3	+34 −10 0=6	+0.4 −0.3	+17 −22 0=11	+0.3 −0.4	0.15	0.07
CF_1	+1 −38 di 11	+0.3 −0.8	0.0	0.0	+48 0=2	+2.1	−50	−17.8	+5 −36 di 9	+1.7 −1.7	+45 −2 0=3	+0.6 −0.8	+46 −1 0=3	+0.6 −0.3	0.13	0.08
CF_2	+6 −26 di 18	+0.8 −0.5	0.0	0.0	+50	+1.6	−50	−21.5	+49 −0 di 1	+1.5	+49 0=1	+1.3	+48 −1 0=1	+1.3 −0.2	0.13	0.08
CF_3≠	+7 −23 di 19	+0.3 −0.5	0.0	0.0	+49	+5.3	−49	−19.7	+49	+1.8	+47 0=2	+1.2	+47 −1 0=1	+1.5 −0.2	0.13	0.08
IVF	+7 −17 di 26	+0.4 −0.4	0.0	0.0	+50	+7.3	−50	−14.3	+50	+5.4	+48 0=2	+1.0	+48 −2	+1.0 −0.4	0.14	0.08
CF_4	+7 −11 di 32	+1 −0.3	+3 0=47	−0.5	+50	+12.0	−46 0=4	+5.8	+50	+4.7	+33 −6 0=11	+0.5 −0.3	+38 −6 0=6	+0.5 −0.3	0.14	0.07
CF_5	+6 −9 di 35	+0.5 −0.2	−24 0=26	−0.4	+50	+9.9	−36 0=14	−2.0	+50	+2.8	+22 −11 0=17	+0.2 −0.2	+24 −5 0=16	+0.3 −0.5	0.14	0.07
Wolferth standard	−42 di 8	−0.4	0.4	0.0	+50	+5.6	−50	−17.8	+1 −49	+1.1 −1.2	+48 0=2	−1.2	+2 −47 0=1	+0.1 −1.1	0.15	0.08
Wolferth apex	+1 −42 di 7	+0.1 −0.4	0.4	0.0	+50	+9.5	−50	−14.6	−50	−6.1	+49 0=1	−1.0	+1 −47 0=2	+0.1 −0.9	0.14	0.08
IVB	+42 di 8	+0.4	0.0	0.0	+50	+9.9	−50	−14.0	+50	+6.2	+48 0=2	+1.0	+47 −3	+0.9 −0.1	0.15	0.08
Whitten	+50	+2.2	−37 0=13	−0.6	+50	+17.2	−30 0=20	−1.5	+50	+4.2	+32 −8 0=10	+0.2 −0.2	+13 −17 0=20	+0.2 −0.3	0.14	0.08

*The signs have the same significance as in Table I, except that the sign ≠ needs further comment, as follows. Because of the unusual contour of the heart, position C_3 coincided with position 4 on the chest of one female. Hence, CR_3 and CF_3 tracings were available on only forty-nine patients of this series.

TABLE IV

SUMMARY OF THE STUDY OF THE STANDARD ELECTROCARDIOGRAMS AND PRECORDIAL LEADS ON FIFTY NORMAL ADULT MALES AND FIFTY NORMAL ADULT FEMALES (CL LEADS WERE NOT STUDIED IN THIS SERIES)*

LEAD	P WAVE		Q WAVE		R WAVE		S WAVE		T WAVE		DEVIATION OF S-T SEGMENT				P-R INTERVAL, AVERAGE DURATION, MM.	AVERAGE DURATION OF QRS, MM.
											FROM P-R		FROM T-P			
	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEFLECTION	AVERAGE AMPLITUDE, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.	DIRECTION OF DEVIATION	AVERAGE DEVIATION, MM.		
I	+100	+0.5	−28 0=72	−0.3	+100	+ 5.6	− 81 0= 19	− 1.5	+ 99 di 1	+2.1	+ 58 − 11 0= 31	+0.2 −0.1	+17 −28 0=55	+0.1 −0.2	0.14	0.08
II	+100	+1.2	−49 0=51	−0.5	+100	+11.6	− 76 0= 24	− 2.4	+ 97 − 1 di 2	+2.6 −1.3	+ 58 − 24 0= 18	+0.4 −0.5	+21 −52 0=27	+0.2 −0.5	0.155	0.08
III	+ 91 − 3 di 6	+0.7 −0.3	−63 0=37	−0.9	+100	+ 7.1	− 66 0= 34	− 2.1	+ 60 − 12 di 28	+1.1 −1.0	+ 47 − 29 0= 24	+0.2 −0.2	+14 −52 0=32	+0.2 −0.4	0.15	0.075
CR$_1$	+ 98 − 1 di 1	+0.9 −0.3	− 1 0=99	−0.0	+ 97 0= 3	+ 4.1	− 99 0= 1	− 9.7	+ 90 − 1 di 9	+2.5 −0.4	+ 97 0= 3	+0.8	+77 − 7 0=16	+0.6 −0.2	0.15	0.08
CR$_2$	+ 98 − 0 di 2	+1.1	0=100	0.0	+100	+ 8.4	−100	−18.1	+100	+8.0	+100	+1.7	+94 − 3 0= 3	+1.3 −0.3	0.15	0.08
CR$_4$#	+ 98 di 1	+1.1	− 1 0=98	−0.2	+ 99	+10.3	− 99	−15.9	+ 99	+8.6	+ 99	+1.6	+92 − 4 0= 3	+1.3 −0.2	0.15	0.08
IVR	+ 99 di 1	+1.1	− 5 0=95	−0.5	+100	+15.5	−100	−12.4	+100	+8.8	+ 97 − 1 0= 2	+1.4 −0.0	+91 − 6 0= 3	+1.0 −0.5	0.15	0.08
CR$_5$	+ 99 iso 1	+1.2	−28 0=72	−0.6	+100	+24.0	− 96 0= 4	− 6.8	+100	+7.7	+ 88 − 6 0= 6	+0.8 −0.4	+71 −17 0=12	+0.6 −0.4	0.15	0.08

CR_6	+ 98 – 1 iso 1	+1.2 –0.6	–62 0=38	–0.8	+100	+12.4	– 73 0= 27	– 3.5	+ 99 poly 1	+5.6	+ 77 – 14 0= 9	+0.6 –0.3	+47 –31 0=22	+0.5 –0.4	0.15	0.075
CF_1	+ 6 – 74 di 20	+0.5 –0.5	0=100	0.0	+ 98 0= 2	+ 2.7	–100	–17.4	– 21 – 65 di 14	+2.0 –1.8	+ 88 – 6 0= 6	+0.6 –0.1	+91 – 3 0= 6	+0.6 –0.2	0.135	0.08
CF_3	+ 19 – 51 di 30	+0.6 –0.5	0=100	0.0	+100	+ 6.5	–100	–24.9	+ 99 di 1	+5.7	+ 99 0= 1	+1.6	+98 – 1 0= 1	+1.6 –0.2	0.135	0.085
CF_3#	+ 20 – 40 di 39	+0.4 –0.5	– 1 0=98	–1.4	+ 99	+ 7.2	– 99	20.4	– 99	+6.2	– 97 0= 2	+1.5	+97 – 1 0= 1	+1.5 –0.2	0.135	0.08
IVF	+ 24 – 33 di 43	+0.4 –0.4	– 3 0=97	–0.8	+100	+ 9.6	–100	–11.4	+100	+6.2	+ 97 – 1 0= 2	+1.1 –0.2	+97 – 2 0= 1	+1.2 –0.1	0.14	0.08
CF_5	+ 26 – 19 di 55	+0.4 –0.3	–19 0=81	–0.6	+100	+14.2	– 96 0= 4	– 6.6	+100	+5.0	+ 73 – 8 0= 19	+0.6 –0.5	+82 – 8 0=10	+0.6 –0.5	0.145	0.07
CF_6	+ 23 – 22 di 55	+4 –0.3	–57 0=43	–0.7	+100	+11.7	– 73 0= 27	– 2.5	+ 98 di 2	+2.8	+ 43 – 24 0= 33	+0.2 –0.2	+60 –14 0=26	+0.3 –0.3	0.145	0.07
Wolferth standard	– 90 di 10	–0.5	0=100	0.0	–100	– 8.2	+100	+29.7	– 1 – 99	+1.1 –6.4	– 98 0= 2	–1.8	– 2 –95 0= 3	+0.1 –1.6	0.155	0.08
Wolferth apex	+ 1 – 91 di 8	+0.1 –0.5	– 1 0=99	–0.3	–100	–12.4	+100	+15.8	–100	–7.4	– 99 0= 1	–1.4	+ 1 –97 0= 2	+0.1 –1.2	0.15	0.08
IVB	+ 91 di 9	+0.5	– 1 0=99	–0.1	+100	+12.8	–100	–15.1	+100	+7.4	+ 98 0= 2	+1.4	+97 – 3	+1.2 –0.1	0.155	0.08
Whitten	+ 99 di 1	+1.5	–79 0=21	–0.8	+100	+19.1	–72 0=28	– 2.4	+ 98 poly 2	+4.7	+ 62 – 21 0= 17	+0.4 –0.3	+36 –34 0=30	+0.3 –0.4	0.14	0.08

*The signs have the same significance as in Table I, except that sign # needs further comment, as follows. Because of the peculiar contour of the heart, position C_3 coincided with position 4 on the chest of one female. Hence CR_3 and CF_3 tracings were available on only ninety-nine patients of this series.

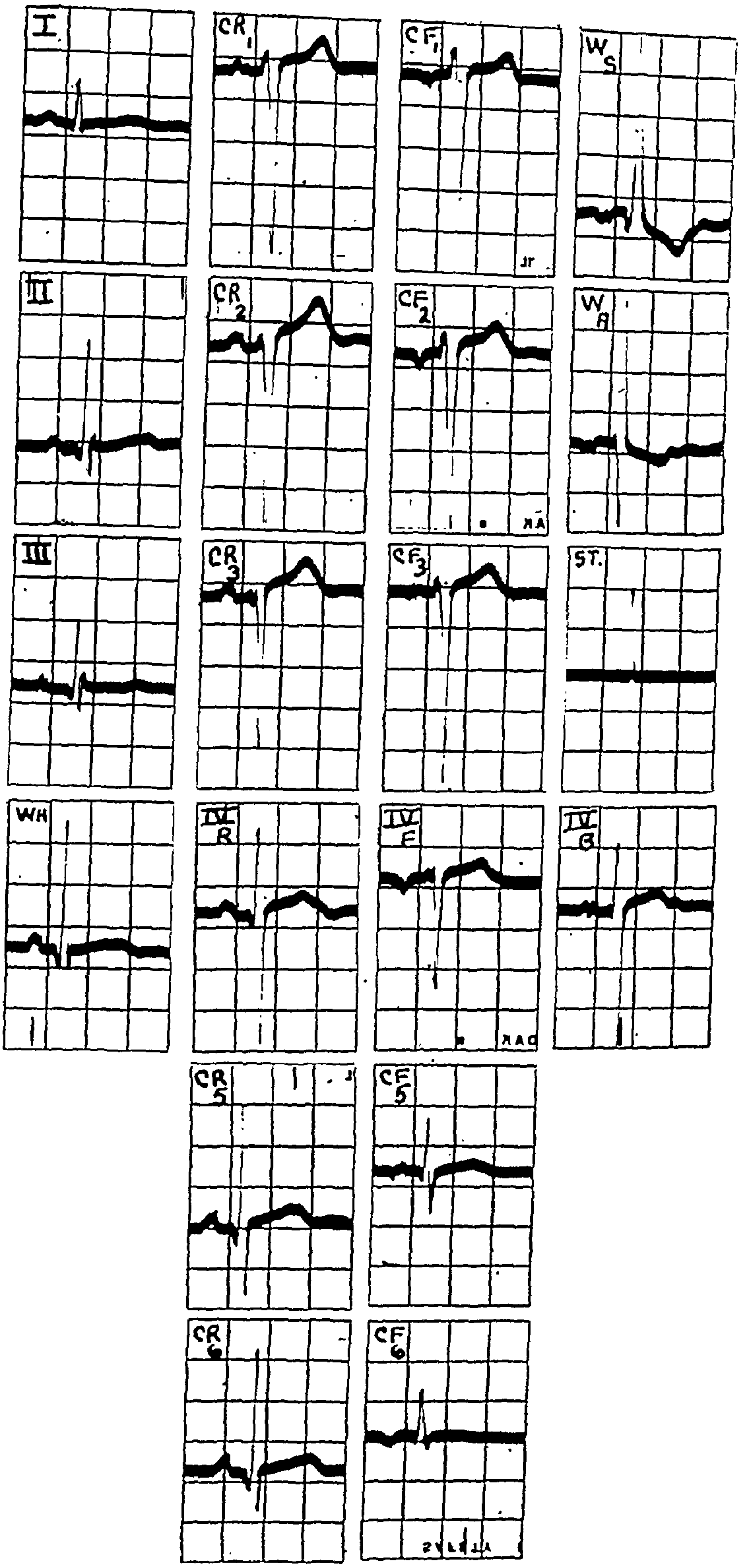


Fig. 7.—Electrocardiogram of a normal man. A true Q wave occurs in IVR, CR5, CR6, CF5, and CF6. A very slight Q wave is present in the Wolferth apex (WA) lead.

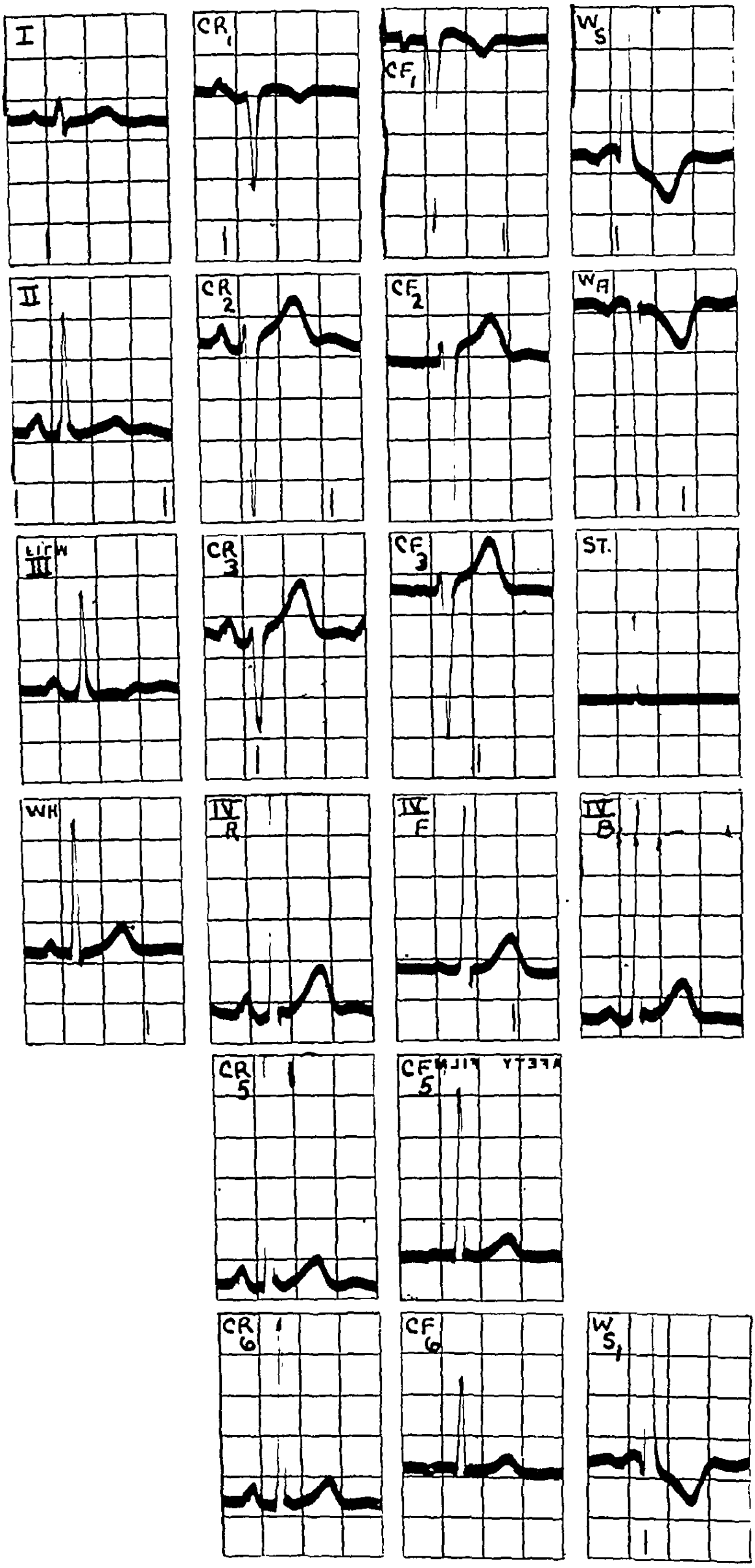


Fig. 8.—Electrocardiogram of a normal man. This illustrates the smallest R wave (so-called Q wave, measuring 1.0 mm.) in the Wolferth standard lead (WS) which was observed in the entire series. Frequently, the R wave (so-called Q wave) in this individual Wolferth standard lead was 2.3 mm. in amplitude (see WS_1) in complexes adjacent to those in which the R wave (so-called Q wave) had an amplitude of only 1 mm. Note the small amplitude of the S wave in Leads IVR and IVF.

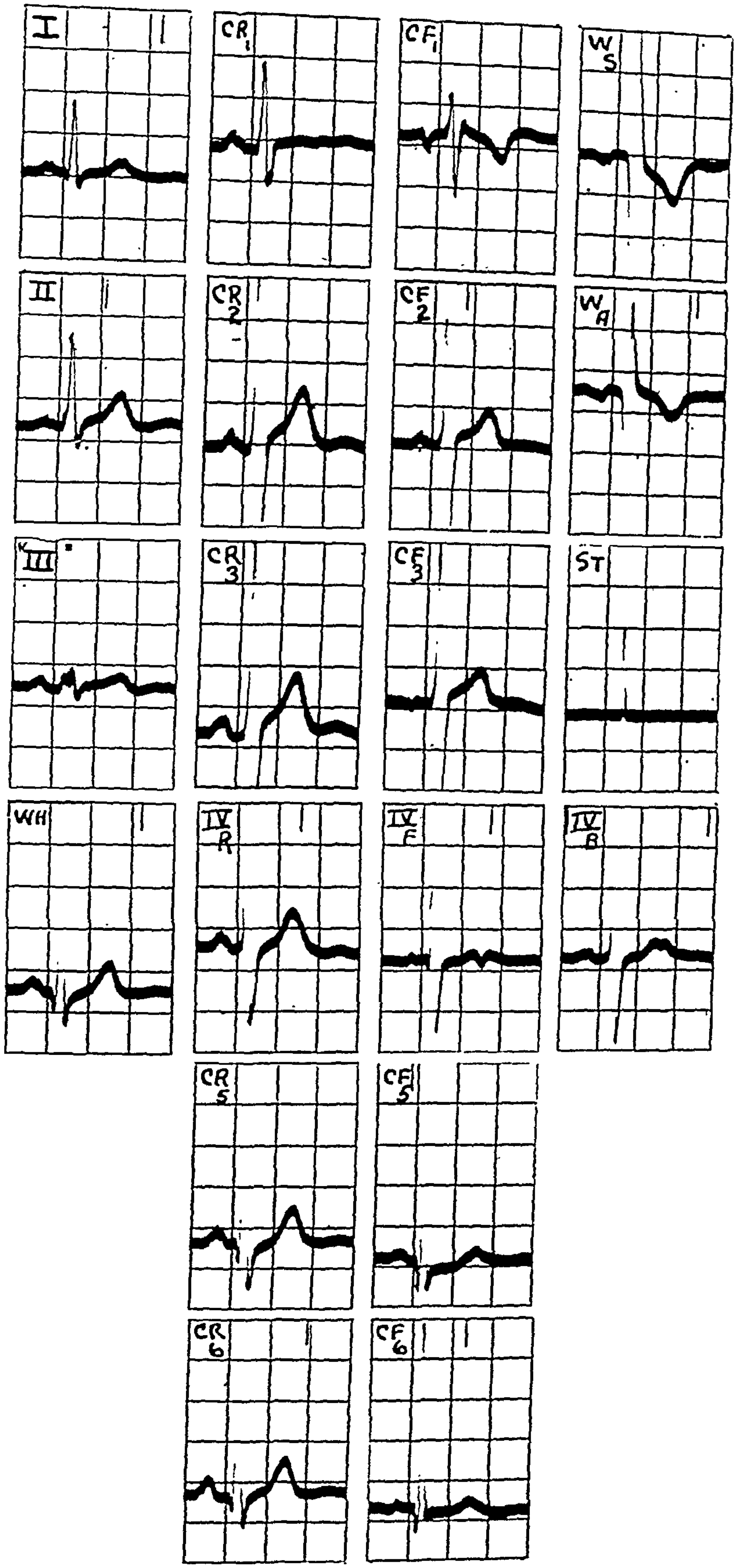


Fig. 9.—Electrocardiogram of a normal man. Leads IVF and IVB illustrate the only frankly notched T waves which were encountered in any of the precordial leads of the entire series. Note that the T wave in the Wolferth lead taken at the apex is only very slightly indented, when compared with IVB.

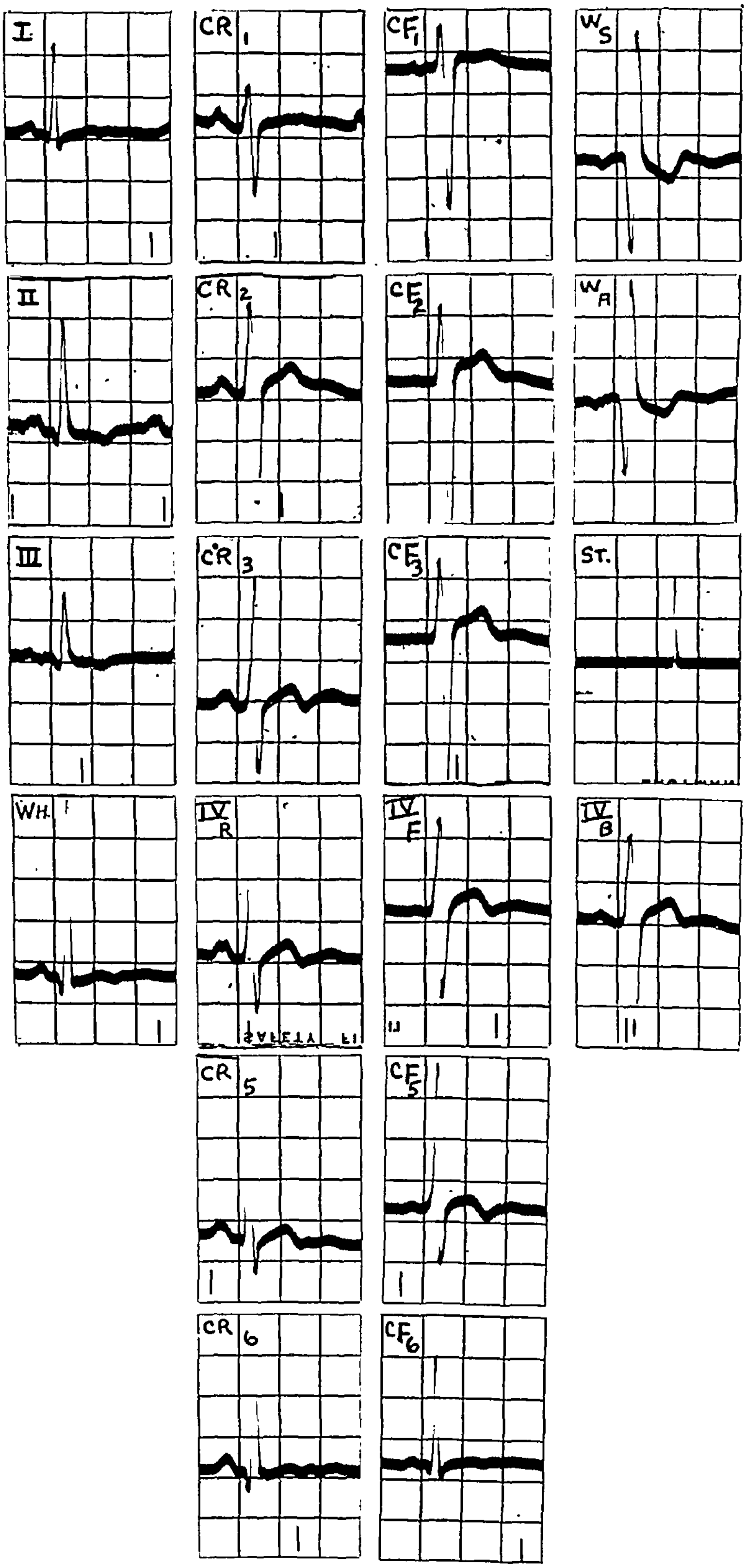


Fig. 10.—Electrocardiogram of a normal man. Note that the T wave is diphasic in Lead I and inverted in Leads II and III, and that it has a diphasic tendency in IVR, IVF, CF_6, Wolferth standard (WS), Wolferth apex (WA), and IVB.

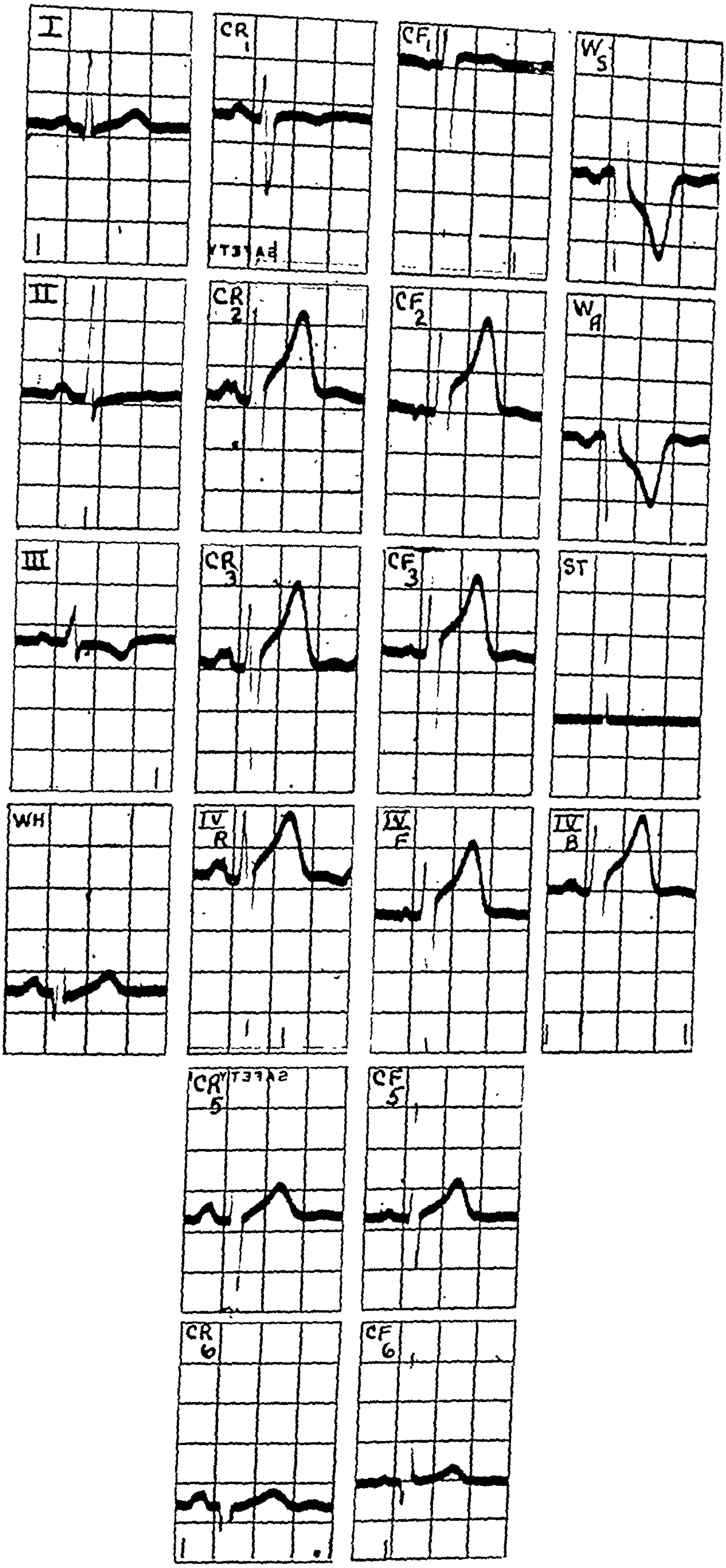


Fig. 11.—Electrocardiogram of a normal man. Observe that the *T* wave is diphasic in Lead II, and that, in Lead III, it is *frankly* inverted, with an *S-T* segment simulating a "*cove-plane*" contour. Note the notching of the P waves, which is most marked in Lead CR_2. The so-called Q wave in the Wolferth leads is smaller at the apex (WA) than in the parasternal (WS) position. Usually, the opposite is true.

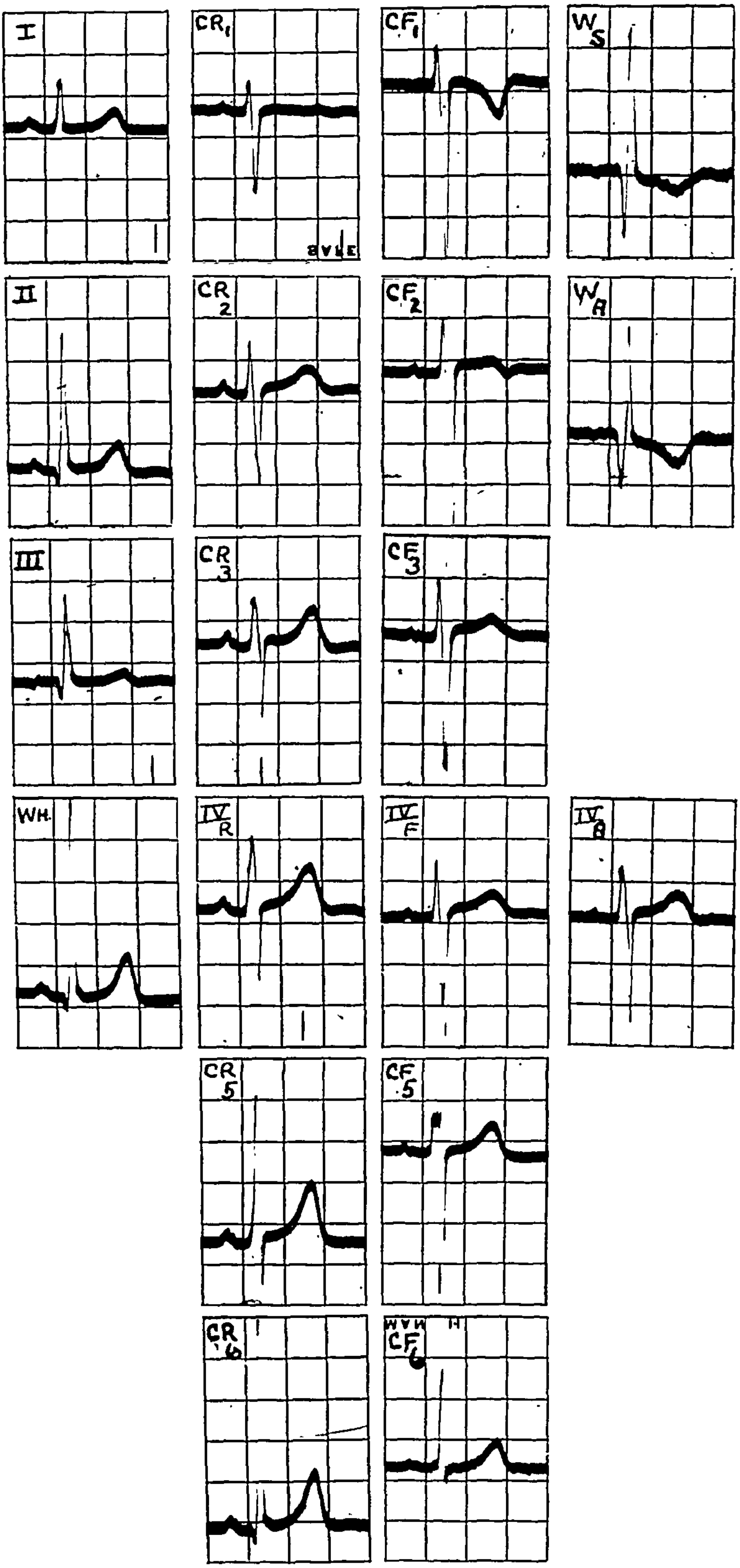


Fig. 12.—Electrocardiogram of a normal woman. Lead CF_2 illustrates the closest approach to an inverted T wave at position 2 which was encountered in the entire series.

MAXIMAL AND MINIMAL MEASUREMENTS OF THE VARIOUS DEFLECTIONS IN THE ST[illegible]

LEAD	P WAVE: MAXIMAL POSITIVE DEFLECTION	P WAVE: MINIMAL POSITIVE DEFLECTION	P WAVE: MAXIMAL NEGATIVE DEFLECTION	P WAVE: MINIMAL NEGATIVE DEFLECTION	Q WAVE: MAXIMAL DEFLECTION	Q WAVE: MINIMAL DEFLECTION	R WAVE: MAXIMAL DEFLECTION
I	0.9	0.2			-0.9	-0.1	+12.20
II	2.0	0.2			-1.8	-0.1	+23.6
III	1.8	0.2	-0.5	-0.1	-3.4	-0.1	+19.1
CR_1	2.1	0.2	-0.3#		0.0	0.0	+21.6
CR_2	2.1	0.4			0.0	0.0	+23.8
CR_3	2.0	0.4			-0.2#		+20.0
IVR	1.8	0.7			-1.0	-0.2	+35.+
CR_5	2.0	0.7			-1.7	-0.1	+35.+
CR_6	1.8	0.5			-2.6	-0.1	+35.+
CF_1	0.5	0.2	-1.7	-0.2	0.0	0.0	+ 9.8
CF_2	1.1	0.1	-1.3	-0.2	0.0	0.0	+16.8
CF_3	1.1	0.1	-1.3	-0.2	-1.6	-1.0	+18.7
IVF	1.1	0.2	-1.2	-0.1	-1.7	-0.4	+30.8
CF_5	1.3	0.2	-0.9	-0.2	-3.0	-0.1	+35.+
CF_6	1.3	0.2	-0.8	-0.2	-2.4	-0.1	+26.0
Wolferth standard	1.3	0.2			0.0	0.0	-23.1
Wolferth apex	1.3	0.2			+0.3#		-35.+
IVB	1.3	0.2			+0.1#		+35.+
Whitten	1.4	0.4			-3.2	-0.1	+35.+

*The T wave of one subject was directed downward in Lead II and had a depth of 1.3 mm. The maximal depth of negative T waves in Lead III, encountered in this group, was 2 mm., and the minimal depth, 0.5 mm. The T wave of one subject in Lead CR_1 was negative and measured 0.4 mm. The maximal depth of negative T waves in Lead CR_1, encountered in this group, was 6.0 mm., and the minimal depth, 0.2 mm. The maximal depth of downwardly directed T waves in the Wolferth standard lead was 15.1 mm., and the minimal depth, 1.7 mm. The corresponding maximal and minimal values for the downwardly directed T waves in the Wolferth apex lead were 15.0 mm. and 1.9 mm., respectively. The sign # indicates that the wave behaved that way in only one instance.

The S-T Segment.—In the precordial leads, the S-T segment usually arises above the isoelectric line, but it may arise at or even below it. The take-off varies from lead to lead, as indicated in the tables.

The P-R Interval.—The P-R interval ranged from 0.12 to 0.20 second. The averages for each lead are indicated in the tables.

The QRS Complex.—The duration of QRS varied from 0.06 to 0.12 second. The woman whose QRS time was consistently 0.12 second is a fine athlete, and her cardiac function is excellent even during very strenuous exertion. Notching and slurring of the QRS complexes were so common in both standard and precordial leads that no significance could be attached to them. The so-called "W" type of QRS complex was seen in Lead III six times (two men and four women), and the "M" type of QRS complex was encountered once, in a man (Lead III).

Axis Deviation.—Frank, marked, right axis deviation was not seen, although four men and four women exhibited slight right axis deviation. Left axis deviation was present and mild in eight men, very definite in two, and quite marked in one. Four women exhibited slight left axis deviation, and two showed only a moderate amount.

OCARDIOGRAMS AND PRECORDIAL LEADS OF FIFTY NORMAL ADULT MALES*

WAVE	T WAVE		S-T FROM P-R				S-T FROM T-P			
MINIMAL DEFLECTION	MAXIMAL POSITIVE DEFLECTION	MINIMAL POSITIVE DEFLECTION	MAXIMAL POSITIVE DEFLECTION	MINIMAL POSITIVE DEFLECTION	MAXIMAL NEGATIVE DEFLECTION	MINIMAL NEGATIVE DEFLECTION	MAXIMAL POSITIVE DEFLECTION	MINIMAL POSITIVE DEFLECTION	MAXIMAL NEGATIVE DEFLECTION	MINIMAL NEGATIVE DEFLECTION
-0.2	4.3	0.4	0.9	0.0	0.3	0.0	0.8	0.0	0.5	0.0
-0.2	6.6	1.0	1.0	0.0	1.0	0.0	1.0	0.0	1.9	0.0
-0.1	2.6	0.3	0.8	0.0	0.6	0.0	1.0	0.0	1.3	0.0
-2.2	9.9	0.4	2.0	+0.2			1.7	0.0	0.1	0.0
-4.5	15.3	3.2	4.0	0.9			3.9	0.4	0.3 #	
-4.6	16.8	1.8	4.0	0.5			3.4	0.0		
-0.6	17.2	1.7	3.5	0.0			3.3	0.0	0.4	0.0
-0.6	16.3	1.6	2.7	0.0	0.4 #		2.0	0.0	0.6	0.0
-0.6	14.0	0.7	2.0	0.0	0.4	0.0	1.4	0.0	1.0	0.0
-6.6	6.7	0.2	1.7	0.0	0.5	0.0	2.0	0.0	0.2	0.0
-7.0	15.5	3.1	3.5	0.2			3.5	0.4		
-6.5	14.9	2.8	3.4	0.5			3.5	0.6		
-1.4	14.3	0.8	3.0	0.3	0.2 #		3.0	0.0		
-1.8	12.3	0.7	2.0	0.0	1.3	0.0	2.2	0.0	1.3	0.0
-0.1	9.6	0.4	1.0	0.0	0.6	0.0	1.0	0.0	0.4	0.0
+4.6					4.0	0.3			3.8	0.0
+0.6					3.5	0.2			3.3	0.1
-0.5	15.2	1.8	3.5	+0.1			3.4	0.1		
-0.3	10.9	1.6	1.4	0.0	-1.5	0.0	1.0	0.0	1.6	0.0

CONCLUSIONS

A conductive electrode paste is necessary in order to obtain satisfactory precordial leads.

CR leads appear to be better than CL leads, which, in turn, are better than CF leads, for the following reasons:

1. CR and CL leads are obtained more conveniently than CF leads. After the three standard leads are derived, CR and CL leads can be taken with the shifting of only one lead wire; obtaining the CF lead necessitates shifting two lead wires.

2. The P wave in CR leads is usually upright. It is almost as frequently upright in CL leads. It is usually diphasic or inverted in CF leads.

3. Usually, the R wave in Lead IVR exceeds the value of R in Lead IVF. Compare the minimal value of the R wave in fifty normal males (Table V) in Lead IVR (+6.3 mm.) with the minimal value for R in IVF (+ 2.8 mm.). Inasmuch as diminution, rather than absence, of the R wave in these leads will constitute a part of the diagnostic criteria in the appraisal of cardiac disease, it is important that the minimal value of R be not too small. Moreover, it will be seen that, in both men and women, the amplitude of the R wave is maintained much better in Leads CR_5 and CR_6 than in Leads CF_5 and CF_6. In women, minimal values

MAXIMAL AND MINIMAL MEASUREMENTS OF THE VARIOUS DEFLECTIONS IN THE ST

LEAD	P WAVE				Q WAVE		R WAVE
	MAXIMAL POSITIVE DEFLECTION	MINIMAL POSITIVE DEFLECTION	MAXIMAL NEGATIVE DEFLECTION	MINIMAL NEGATIVE DEFLECTION	MAXIMAL DEFLECTION	MINIMAL DEFLECTION	MAXIMAL DEFLECTION
I	1.1	0.2			−0.6	−0.1	+11.5
II	2.6	0.4			−0.7	−0.1	+21.9
III	1.8	0.2			−4.6	−0.1	+17.3
CR_1	2.2	0.3			0.0	0.0	+8.1
CR_2	2.7	0.3			0.0	0.0	+13.6
CR_3	2.4	0.4			0.0	0.0	+17.1
IVR	2.4	0.5			0.0	0.0	+35.+
CR_5	2.3	0.4			−1.1	−0.1	+35.+
CR_6	2.1	0.4	0.6#		−1.8	−0.1	+35.+
CF_1	0.3#		−2.0	−0.2	0.0	0.0	+ 6.5
CF_2	2.6	0.3	−1.7	−0.1	0.0	0.0	+10.7
CF_3	0.6	0.2	−1.4	−0.1	0.0	0.0	+13.0
IVF	0.6	0.3	−1.1	−0.2	0.0	0.0	+39.0
CF_5	0.6	0.2	−0.9	−0.2	−1.0	−0.1	+24.9
CF_6	1.8	0.2	−0.4	−0.1	−1.4	−0.1	+30.4
Wolferth standard	0.0	0.0	−1.2	−0.2	0.0	0.0	−11.6
Wolferth apex	0.1	0.0	−1.0	−0.2	0.0	0.0	−35.4
IVB	1.0	0.1			0.0	0.0	+37.3
Whitten	1.8	0.1			−2.1	−0.1	+31.6

*The maximal depth of negative T waves in Lead III, encountered in this group, was 1.6 mm., and the minimal depth 0.4 mm. The corresponding values of negative T waves in Lead CF_1 were 3.9 mm. and 0.3 mm. respectively. The maximal depth of downwardly directed T waves in the Wolferth standard lead was 7.5 mm., and the minimal depth, 1.6 mm. The corresponding maximal and minimal values for the downwardly directed T waves in the Wolferth apex lead were 11.2 mm. and 1.8 mm., respectively. The sign # indicates that the wave behaved that way in only one instance. The "pathologic," upright T wave in the Wolferth standard lead was not present in a recheck series.

of the R wave are approximately the same in Leads IVR and IVF. In women, minimal values of the S wave in Leads IVR and IVF are essentially the same.

4. The T wave has a greater amplitude in Lead IVR (average +8.8 mm. in both sexes; minimal +1.7 mm. in men) than it has in Lead IVF (average +6.2 mm. in both sexes; minimal +0.8 mm. in men). Inasmuch as it will be necessary to evaluate low voltage of the T waves in these leads in the diagnosis of cardiac disease, it is desirable that the minimal values be not too low. Similarly, the amplitude of the T wave in Leads CR_5 and CR_6 is maintained better than it is in Leads CF_5 and CF_6.

5. In one instance, the T wave approached negativity in Lead CF_2. This never occurred in Lead CR_2.

6. CR and CL leads frequently, but not constantly, exhibit lesser degrees of deviation of the S-T segments from the level of the P-R and T-P segments than do CF leads.

7. In technical studies such as this, the importance of a perfectly level base line cannot be overemphasized. It was observed throughout this study that, during the taking of CR, CL, and CF leads at a given

:DIOGRAMS AND PRECORDIAL LEADS OF FIFTY NORMAL ADULT FEMALES*

E	T WAVE		S-T FROM P-R				S-T FROM T-P			
IIN-IMAL FLEC-TION	MAX-IMAL POSI-TIVE DEFLEC-TION	MIN-IMAL POSI-TIVE DEFLEC-TION	MAX-IMAL POSI-TIVE DEFLEC-TION	MIN-IMAL POSI-TIVE DEFLEC-TION	MAX-IMAL NEGA-TIVE DEFLEC-TION	MIN-IMAL NEGA-TIVE DEFLEC-TION	MAX-IMAL POSI-TIVE DEFLEC-TION	MIN-IMAL POSI-TIVE DEFLEC-TION	MAX-IMAL NEGA-TIVE DEFLEC-TION	MIN-IMAL NEGA-TIVE DEFLEC-TION
- 0.1	3.6	0.4	0.8	0.0	0.2	0.0	0.1	0.0	0.5	0.0
- 0.1	4.7	0.3	0.5	0.0	0.8	0.0	0.1	0.0	1.9	0.0
- 0.1	2.4	0.2	0.4	0.0	1.0	0.0	0.3	0.0	1.5	0.0
- 3.8	4.6	0.1	1.4	0.0			0.9	0.0	1.0	0.0
- 6.6	12.1	2.3	2.6	0.1			2.1	0.0	0.6	0.0
- 4.9	11.8	2.6	2.1	0.2			1.6	0.0	0.4	0.0
- 2.1	13.6	2.6	2.3	0.0	0.1	0.0	1.8	0.0	1.1	0.0
- 0.4	13.0	2.0	1.4	0.0	1.2	0.0	1.0	0.0	1.5	0.0
- 0.4	10.7	1.6	0.9	0.0	1.3	0.0	0.9	0.0	2.2	0.0
- 6.7	3.9	0.3	1.3	0.0	0.1	0.0	1.7	0.0	0.3	0.0
-12.0	10.1	1.7	2.4	0.0			2.5	0.0	0.2	0.0
- 8.1	9.3	1.2	2.5	0.0			2.4	0.0	0.2	0.0
- 2.2	9.3	1.3	2.6	0.0			2.0	0.2	0.2	-0.1
- 8.6	8.9	1.2	1.4	0.0	0.8	0.0	1.4	0.0	1.2	-0.0
- 0.1	6.1	0.6	0.7	0.0	0.7	0.0	1.0	0.0	0.9	0.0
+ 8.1	1.1#				2.2	0.0	0.2	0.0	2.0	0.0
+ 4.6					2.2	0.0	0.1	0.0	2.0	0.0
- 5.2	11.8	1.9	2.4	0.0			1.9	0.1	0.2	0.1
- 0.1	7.8	1.3	0.6	0.0	-0.6	0.0	0.4	0.0	1.1	0.0

position, it was frequently more difficult to achieve a perfectly level base line when the left leg was the indifferent electrode (CF leads) than when either arm was used (CR or CL leads).

The range of normal for the various deflections varies with the position of the indifferent electrode and with the sex of the subject. Therefore, the separate standards of normal variability established for each sex by this study are of vital importance when the presence or absence of abnormality is being considered. Of the quantitative determinations made on multiple chest lead electrocardiograms obtained from one hundred normal adults (fifty men and fifty women), the following have particular clinical significance: Minimal values of the R wave in Leads IVR and IVF for men are +6.3 and +2.8 mm., respectively; corresponding values for women are +1.1 and +1.2 mm., respectively. Minimal values of the S wave in Leads IVR and IVF for men are –0.6 and –1.4 mm., respectively; corresponding values for women are –2.1 and –1.2 mm., respectively. The minimal height of the T wave in Leads IVR and IVF for men is +1.7 and +0.8 mm., respectively; corresponding values for women are +2.6 and +1.3 mm., respectively.

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PHONOCARDIOGRAPHIC STUDIES OF EARLY RHEUMATIC MITRAL DISEASE

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The studies which form the basis of the present report were performed in an attempt to elucidate the physiologic mechanism of certain auscultatory signs which are associated with early rheumatic mitral disease. At the House of the Good Samaritan, where we have had an opportunity to observe a large number of children during the first year of their rheumatic fever, it has been our experience that the physical signs of early involvement of the mitral valve show the following characteristics:

There is always an apical systolic murmur, which is of at least moderate intensity and is constant. The murmur sometimes begins with a definite first heart sound. Often the first sound is completely or partly masked, so that the onset of ventricular systole is marked by the beginning of the murmur. Although diastole may be entirely silent, an extra, or third, sound in the early part of diastole, or a diastolic murmur, is frequently heard. The diastolic murmur is often discrete, and starts with a third sound or at about the time in diastole when a third sound would normally occur.

Occasionally, the diastolic murmur seems to be hardly more than a slightly prolonged third sound, so that its exact differentiation from the latter may be difficult.

Third sounds and discrete diastolic murmurs are heard more often when the patient has little or no cardiac enlargement, and a mild or quiescent rheumatic infection. When the disease is more severe, with tachycardia and, usually, moderate to marked cardiac enlargement, the diastolic murmur is more likely to be a poorly defined rumble of low intensity. A few severely ill patients, with rapid heart rates (140-150), have an apparent presystolic murmur which, however, lacks the crescendo quality associated only with definite mitral stenosis. Rarely, this murmur is accompanied by a thrill.

Since it is generally accepted that the systolic murmur which is associated with disease of the mitral valve is caused by mitral regurgitation, we have confined our studies to the sounds and murmurs occurring during diastole. That the diastolic murmur, or rumble, of early rheumatic mitral involvement is seldom indicative of anatomic mitral stenosis was pointed out by Bland, White, and Jones,[1] who found that patients who died of rheumatic fever within one year of its onset rarely, if ever, had any narrowing, or even appreciable deformity, of the mitral valve.

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They suggested that the murmur might be caused, in these special instances, either by a "relative stenosis of the orifice in relation to the dilated ventricular cavity," or by "vibrations set up by the diastolic filling of a capacious cavity with relaxed and relatively atonic walls."

It seemed to us that a better understanding of the mechanism of these diastolic sounds might be obtained by recording and correlating them with various other events in the cardiac cycle. Therefore, phonocardiograms were taken synchronously with electrocardiograms, or tracings of the venous pulse, or apical pulsations. An electrical method was used exclusively.*

Studies were made of fifteen unselected patients with mitral involvement who had been ill with rheumatic infection for less than one year. Their ages varied from four to twelve years. In each instance the phonocardiograms were taken after the results of a careful clinical examination had been recorded.

These patients may be divided into three groups, according to the auscultatory signs at the mitral area: (1) Five patients had a systolic murmur and a definite, extra heart sound early in diastole. In all of these cases the rheumatic infection had become either quiescent or low-grade. Their hearts were either normal in size or only slightly enlarged. (2) Nine patients had a systolic murmur and a definite diastolic rumble (without a presystolic crescendo phase). The first three of this group had only a low-grade rheumatic infection, and hearts which were either normal in size or slightly enlarged. The remaining six patients were moderately to severely ill, and their hearts were moderately to greatly enlarged. (3) One patient had a systolic and a presystolic murmur; the latter had no crescendo quality, but was acompanied by a thrill. This patient was extremely ill, and had a very large heart.

PHONOCARDIOGRAPHIC OBSERVATIONS

The phonocardiograms of the five patients in the first group showed a first heart sound, followed by a systolic murmur, a second heart sound, and, in diastole, an extra sound. In three of the five patients this extra sound occurred during the fall of the V wave of the venous pulse. This time relation indicated that the extra sound was a normal third heart sound.[2, 3, 4] In the remaining two patients of the first group, the vibrations composing the extra sound were similar in appearance to those in the previous records, except that they occurred at a shorter interval after the second sound, and synchronously with the apex of the V wave of the venous pulse (Fig. 1). This suggests that the extra sound in these two cases might have been caused by the opening snap of the mitral valve, and therefore was not a real third heart sound. However, it has been shown that the isometric relaxation phase of the left ventricle may be shortened when there is mitral regurgitation.[5] Under such circumstances, the third sound, which is produced during rapid

*All of the tracings which were made in this investigation were registered by electrical mechanisms and their associated optical systems. The Sanborn Stetho-Cardiette which was employed contains two electrical recording systems. One of the systems is especially suited to the graphic registration of heart sounds. The second system is designed specifically to record the electrocardiogram. A special type of crystal microphone is employed to convert the pressure variations of the venous pulse or apical beat into corresponding electrical impulses, which are then recorded by the cardiograph portion of the Stetho-Cardiette.

inflow into the left ventricle, might not show its usual relation to the V wave of the venous pulse, for the latter is associated with pressure changes in the right ventricle. Therefore, in order to ascertain the nature of the extra sound in these cases, it was necessary to take phonocardiograms simultaneously with records of the apical pulsation. In both cases the extra sound occurred synchronously with the phase of rapid inflow into the left ventricle, which is indicated by the R. I. peak* in the apical pulse tracing (Fig. 2). We have concluded, therefore, that, in these two cases, as well as in the previous ones, the extra sound was a real third heart sound.

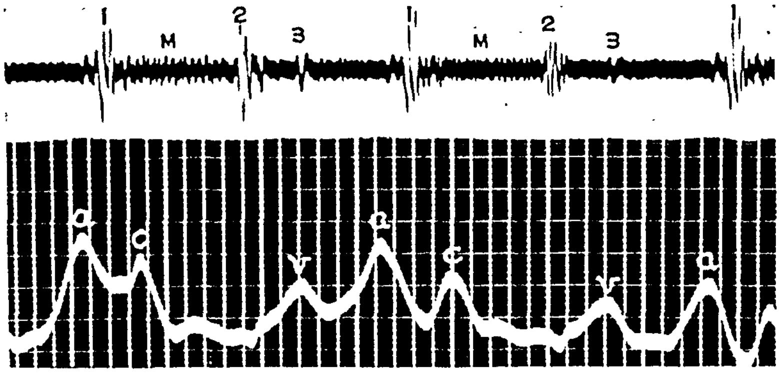

Fig. 1.—Simultaneously recorded phonocardiogram and venous pulse. The third sound appears synchronously with the apex of the V wave.

A.

B.

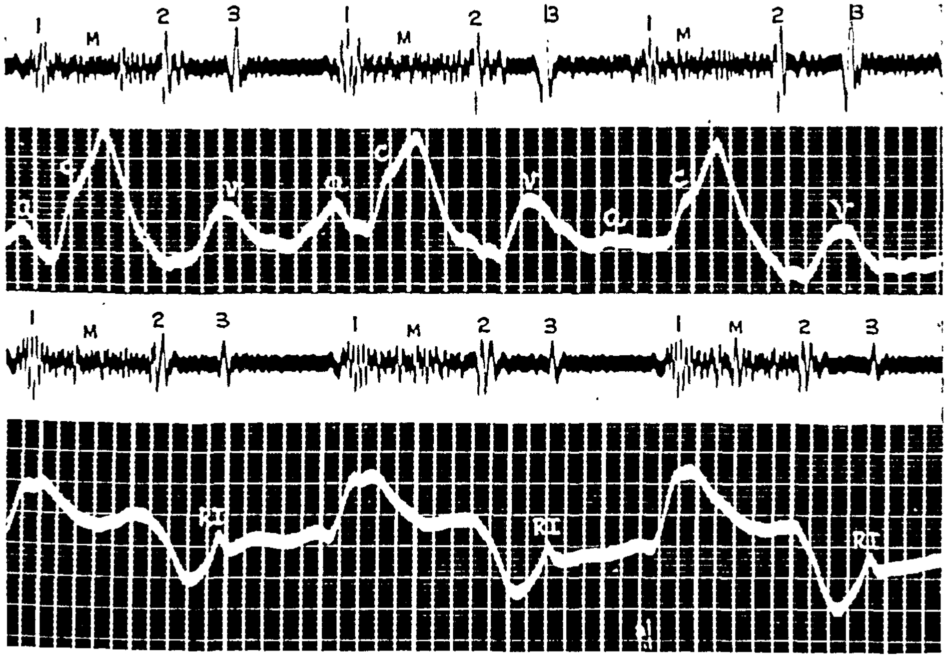

Fig. 2.—*A*, simultaneously recorded phonocardiogram and venous pulse. The third sound appears synchronously with the apex of the V wave. *B*, simultaneously recorded phonocardiogram and apical pulse in the same patient. The third sound appears synchronously with rapid inflow (R. I.) into the left ventricle.

*This wave has been referred to as "the protodiastolic wave" by Bridgman,[6] and "the rapid positive wave" by Orías and Braun-Menéndez.[4]

In some of the cases the phonocardiographic records showed vibrations which occurred about 0.10 second after the beginning of the P wave of the electrocardiogram. It is likely that they represent auricular sounds, in spite of the fact that they were inaudible (Fig. 3).

The phonocardiograms of the second group of nine patients (those with both systolic and diastolic murmurs by auscultation) were not entirely alike. All showed the first sound, followed by a systolic murmur and a second sound, but the graphic phenomena during diastole were variable, and the variation apparently depended on the length of diastole.

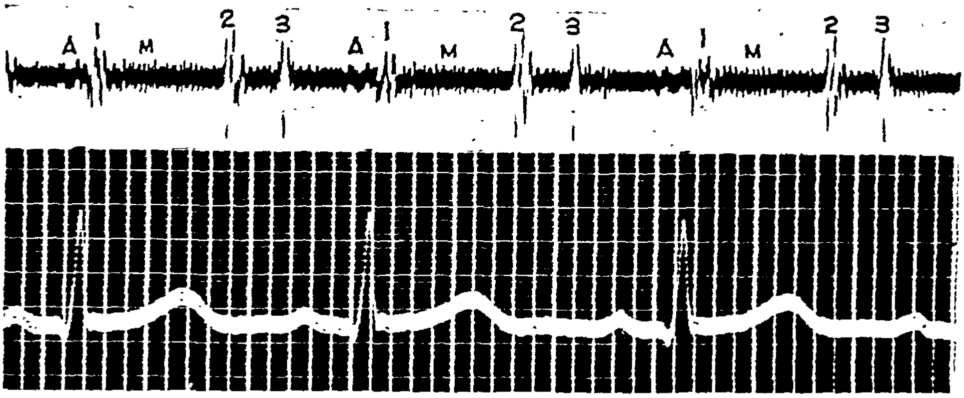

Fig. 3.—Simultaneously recorded phonocardiogram and electrocardiogram. A group of vibrations (*A*) appears about 0.10 second after the beginning of the P wave.

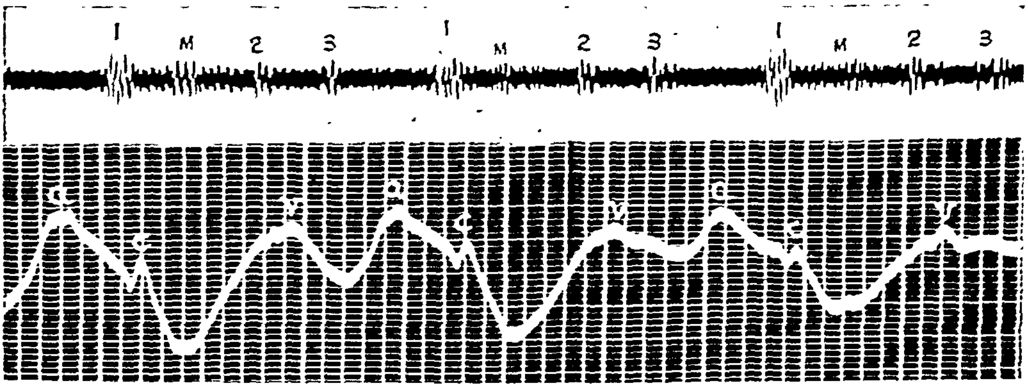

Fig. 4.—Simultaneously recorded phonocardiogram and electrocardiogram. A group of vibrations (*3*) occurs synchronously with the fall of the V wave.

The *phonocardiograms of the first patient,* whose heart rate was relatively slow (under 100), showed one group of oscillations during diastole. These occurred during the fall of the V wave of the venous pulse and were synchronous with the R. I. peak of the apical pulsation, and therefore coincided with the phase of rapid inflow. It is apparent that these vibrations occupied the same location in diastole as the normal third sound. Furthermore, the appearance of these vibrations was similar to that of the third sound in the phonocardiograms of the first group of patients, except that they were of slightly longer duration. (The simultaneously recorded phonocardiogram and venous pulse tracing are shown in Fig. 4.)

The next two patients had slightly more rapid heart rates (about 100). Their phonocardiograms showed, in diastole, two groups of vibrations. The first set of vibrations, as in the previous case, was a prolonged third sound. The second group of vibrations, which followed the first by a very short interval, occurred about 0.10 second after the beginning of the P wave of the electrocardiogram. This sound, which was produced during auricular systole, had the same time relations and phonocardiographic characteristics as the auricular sound (see Fig. 5).

In these phonocardiograms, the presence or absence of vibrations caused by auricular systole was related to the length of diastole. When diastole was relatively long, the vibrations were very small or did not appear, because most of the blood had already passed from the auricle into the ventricle before auricular systole occurred. When diastole was shorter, sufficient blood remained in the auricle to be expelled forcibly into the ventricle by auricular systole. This resulted in further distention of the ventricular walls and produced larger auricular sound vibrations.*

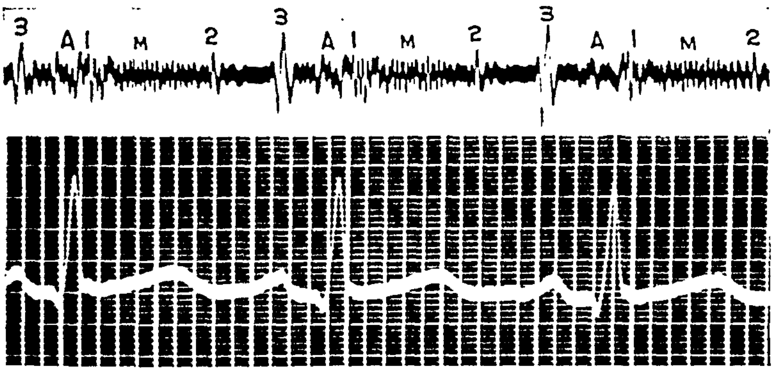

Fig. 5.—Simultaneously recorded phonocardiogram and electrocardiogram. There are two groups of vibrations in diastole, one caused by the third sound (*3*), the other by the auricular sound (*A*).

There were five patients with tachycardia (about 130) whose phonocardiograms showed only one group of oscillations during diastole, and these were of relatively large amplitude (Fig. 6). Phonocardiograms which were taken simultaneously with the venous pulse or apical pulsation showed that in these cases, in which diastole was shortened, rapid inflow and auricular systole occurred at the same moment. (The simultaneously recorded phonocardiogram and venous pulse in one of these cases is shown in Fig. 7.) It is therefore likely that in these patients the single large group of oscillations was the result of ventricular distention produced by the combined effect of rapid inflow and auricular systole.

Further evidence that this interpretation is correct is presented by the record of a patient who had sinus arrhythmia and a prolonged

*It has been shown that that portion of the auricular sound which can be recorded from the precordial area is caused by vibrations set up in the ventricular walls by the impact of the blood which is forced into the ventricle by auricular contraction.[7]

auriculoventricular conduction time (Fig. 8). It is apparent that, depending on the duration of diastole, there are (1) two definitely separate groups of vibrations, (2) a single but prolonged vibration period with one group of vibrations immediately following the other, or (3) a shorter period of somewhat larger vibrations caused by superimposition of one group on the other.

Thus it appears that the diastolic rumble in these nine patients with early rheumatic mitral disease corresponded to (a) one group of vibrations which, phonocardiographically, was a prolonged third sound, (b) two successive, but separate, groups of vibrations, the first of which occurred when the ventricle was being distended by rapid inflow during early diastole, and was therefore a prolonged third sound, and the second when the ventricle was distended by auricular systole, and was therefore an auricular sound, or (c) one large group of vibrations caused by summation of the oscillations of the third and auricular sounds.

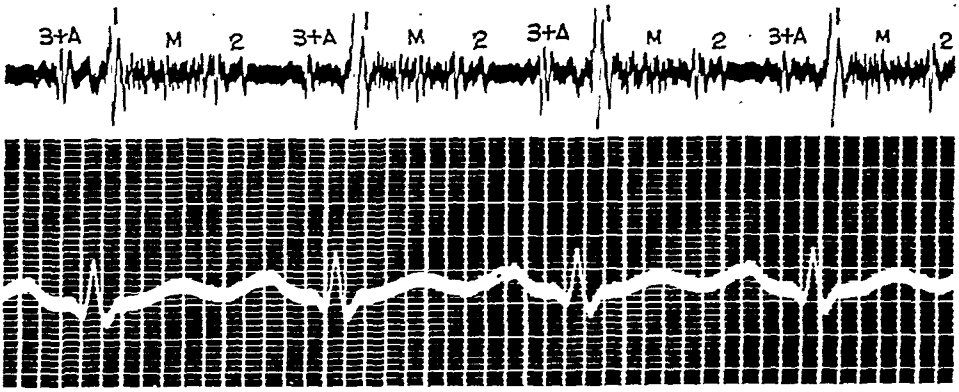

Fig. 6.—Simultaneously recorded phonocardiogram and electrocardiogram. In diastole there appears one large group of vibrations about 0.10 second after the beginning of the P wave. This is produced by the combined third (*3*) and auricular (*A*) sounds.

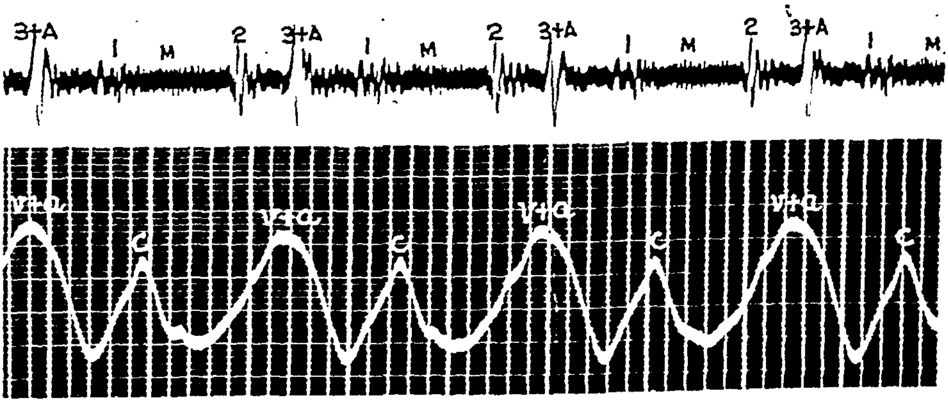

Fig. 7.—Simultaneously recorded phonocardiogram and venous pulse. The venous pulse shows a summation of the V and A waves. The phonocardiogram shows one large group of vibrations in diastole which represents a combination of the third (*3*) and auricular (*A*) sounds.

One patient in the third clinical group was separated from the others because his diastolic murmur seemed to be presystolic in time and was

accompanied by a thrill. However, phonocardiograms which were taken simultaneously with the venous pulse or apical pulsation showed that, as in the previous patients, the diastolic vibrations were caused by combined third and auricular sounds.

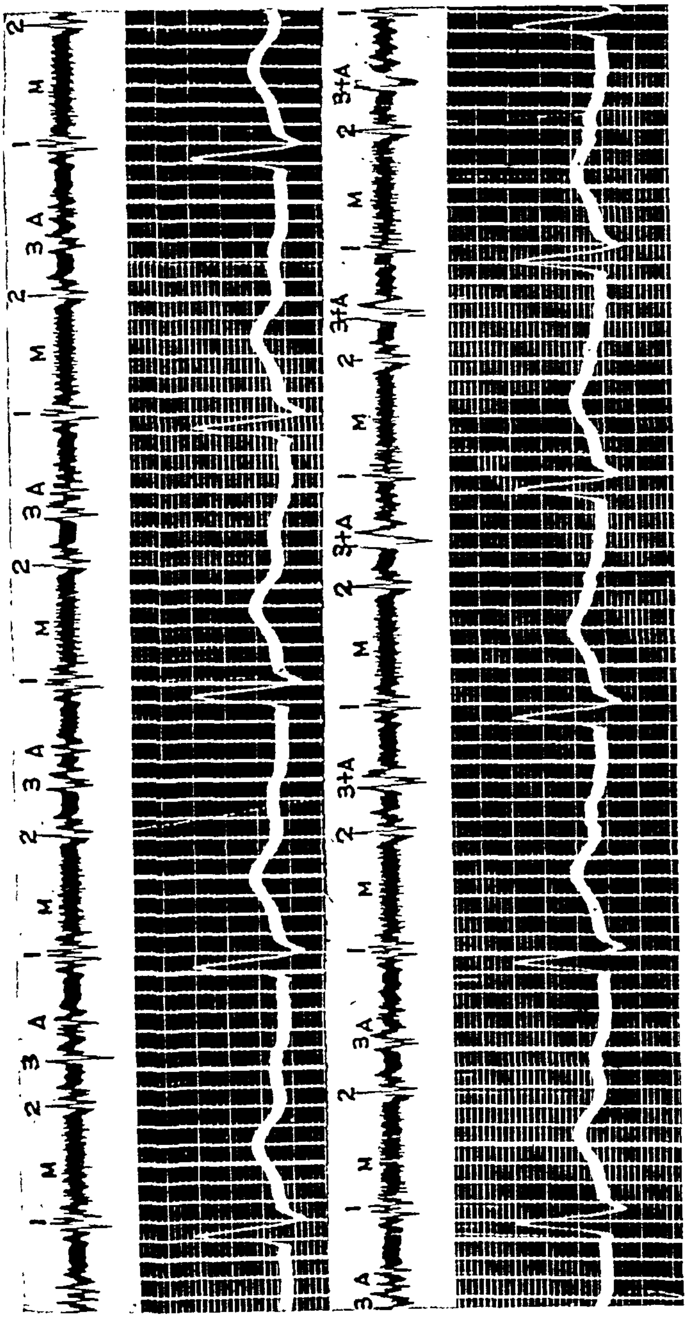

Fig. 8.—Simultaneously recorded phonocardiogram and electrocardiogram (the upper and lower records are continuous). The record shows the auricular sound either (*A*) definitely separated from the third sound (*3*), immediately after the third sound, or superimposed upon the third sound, depending upon the duration of diastole.

DISCUSSION AND CONCLUSIONS

These phonocardiographic studies show that the third sound, which is commonly present in normal children, is unusually prominent in some patients with early rheumatic mitral disease, and may even be

sufficiently prolonged to produce a diastolic rumble. The frequent occurrence of the third sound in normal children may be explained by their relatively thin ventricular and chest walls. The unusual prominence of the third sound, and its frequent prolongation into a rumble, in patients with early rheumatic mitral disease may be related to two additional factors. The first is the effect of mitral regurgitation. This increases the amount of blood which flows into the left auricle, and thereby greatly augments the intra-auricular pressure. As a result, a larger amount of blood passes with increased force into the left ventricle during rapid inflow, and this produces a degree of distention of its walls which is greater than normal. The second factor may be a decreased tonicity of the ventricular musculature consequent to the rheumatic infection.

In patients with slightly increased heart rates, the presence of an audible auricular sound following quickly after a somewhat prolonged third sound enhances the auditory effect of a rumble.

When there is considerable tachycardia, auricular contraction may occur simultaneously with rapid inflow, so that their effects are combined. The resulting overdistention of the ventricle produces vibrations which represent superimposed third and auricular sounds. These relatively strong vibrations, together with a short diastole, again produce the acoustic effect of a rumble.

SUMMARY

Clinical experience has shown that patients with rheumatic mitral valve involvement of less than one year's duration always have an apical systolic murmur of at least moderate intensity. In addition, they frequently have in diastole a moderately loud extra sound or a rumbling murmur.

Phonocardiograms were taken synchronously with electrocardiograms or tracings of the venous pulse or apical pulsations in fifteen unselected cases of early rheumatic mitral involvement. From these studies we have concluded that:

1. The audible extra sound appears, in the phonocardiogram, as a series of vibrations which occur at the moment when the left ventricle is distended by rapid inflow, and is therefore a real third sound.

2. In some cases, prolongation of the vibrations of the third sound may produce the acoustic effect of a rumble.

3. In other cases, the vibrations of the auricular sound which occur very shortly after, or are superimposed upon, prolonged vibrations of the third sound enhance the acoustic effect of a rumble.

We are grateful to Mr. Morris Rappaport, of the Sanborn Company, for technical assistance.

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RESPONSE TO RENIN OF UNANESTHETIZED NORMAL AND NEPHRECTOMIZED RATS*

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IT WAS shown by Tigerstedt and Bergmann,[1] in 1898, that the pressor response of rabbits to renin was greater after the animals had been nephrectomized. It was further demonstrated by Merrill, Williams, and Harrison,[2] who worked with rats, that, by waiting two or three days after nephrectomy, both the degree and duration of the renin pressor effects were enhanced. All of these experiments were performed on anesthetized animals, however, and, since Shaw[3] believed that this factor influenced the renin effect, it seemed desirable to repeat the work of Merrill, Williams, and Harrison on unanesthetized animals.

METHOD

Williams, Harrison, and Grollman's apparatus[4] was used for taking serial systolic pressure readings on rats at frequent intervals. Unanesthetized animals were trained to the routine and taught to remain quiet while their pressures were being taken. After control pressures were recorded, 1 c.c. of renin† was administered intraperitoneally. The rats' pressures were followed at one- or two-minute intervals for the first ten minutes, once or twice again during the first hour, and frequently during successive hours. Inasmuch as the method requires that the rats be warmed in order to produce adequate peripheral vasodilation, care was taken to establish a constant, slow heating time, and to avoid overheating.

The rats chosen were males, weighing from 230 to 280 Gm., and nonpregnant females which weighed 180 to 220 Gm.; ten normal and nine nephrectomized animals were used. Comparison of the same animal's response to renin before and after nephrectomy was made in several instances. Nephrectomy was performed under light ether anesthesia through flank incisions; the animals resumed their normal behavior within half an hour after operation. The animals responded but little, or not at all, to renin for the first few hours after nephrectomy, and it was therefore decided to wait a minimum of nine hours after operation before making the injections. Control pressures after nephrectomy were of the same order as those prior to operation, averaging 118 mm. of mercury in normal animals and 115 mm. in nephrectomized animals.

RESULTS

As shown by the charts, nephrectomized animals differed decidedly from normal ones in their responses to renin. This was true of both the intensity and duration of the effect. The blood pressures of the normal animals rose an average of 30 mm. of mercury within from four

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†Renin was prepared from hog kidneys by a modification of the method of Grossman.[5] To the dried powder which remained after alcohol and ether extractions, there was added 1 c.c. of normal saline for each gram of original cortex. This was allowed to stand in the refrigerator for twenty-four hours and was then centrifuged. The supernatant fluid was a clear, reddish-brown liquid which possessed a rapid pressor action, with no initial depressor effect, when injected into the aortas of anesthetized rats, and when injected intraperitoneally into unanesthetized rats.

to seven minutes after the injection of renin; the highest rise was 44 mm. By contrast, the nephrectomized animals responded with an average rise, in the same period, of 58 mm.; one animal's blood pressure rose 108 mm. of mercury above its control level. The average, immediate, blood pressure rise of the nephrectomized rats was therefore almost twice that of the normals.

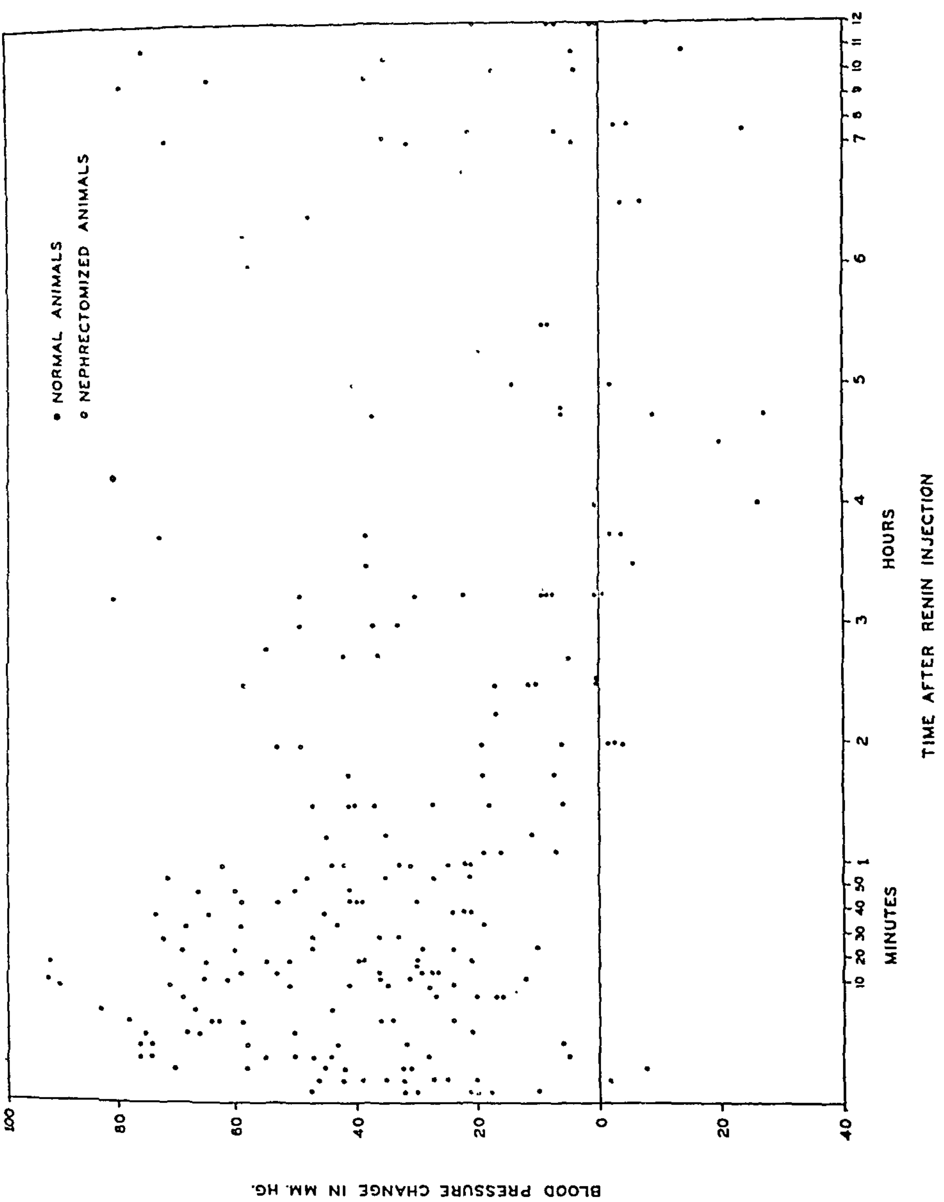

Fig. 1.—Each point represents the change in blood pressure of one rat, at the time designated, after intraperitoneal injection of 1 c.c. of renin. The zero line indicates the control pressure before injection.

After these prompt initial elevations, the pressures of the normal animals subsided to approximately preinjection levels within two or three hours, but the blood pressures of the nephrectomized animals did not return to normal levels in less than five hours, and frequently remained elevated for as long as twelve hours. Occasionally, an animal died twenty hours, or more, after the injection, with all recorded pres-

sures still above the control level. When an average was taken of the amount of blood pressure change during the period from four to twelve hours after nephrectomy, it was found that the pressures were still 39 mm. of mercury above the preinjection level. At this time the blood pressures of the rats with intact kidneys were almost normal.

COMMENT

These observations indicate that the increased sensitivity of nephrectomized animals to renin, which has been observed by others,[1, 2] is not related to anesthesia. In fact, the opportunity for prolonged observation of the unanesthetized animal makes the increase in sensitivity seem more pronounced than that reported by Merrill, Williams, and Harrison.[2] The experiments suggest also that normal renal tissue may play some role with regard to the fate in the body of artificially administered renin. The fact that rats are inexpensive, and that there is a simple and direct method of measuring their blood pressure frequently, a method which enables one to measure the pressures of relatively large numbers of animals in a short period of time, makes their use for the assay of kidney extracts feasible.

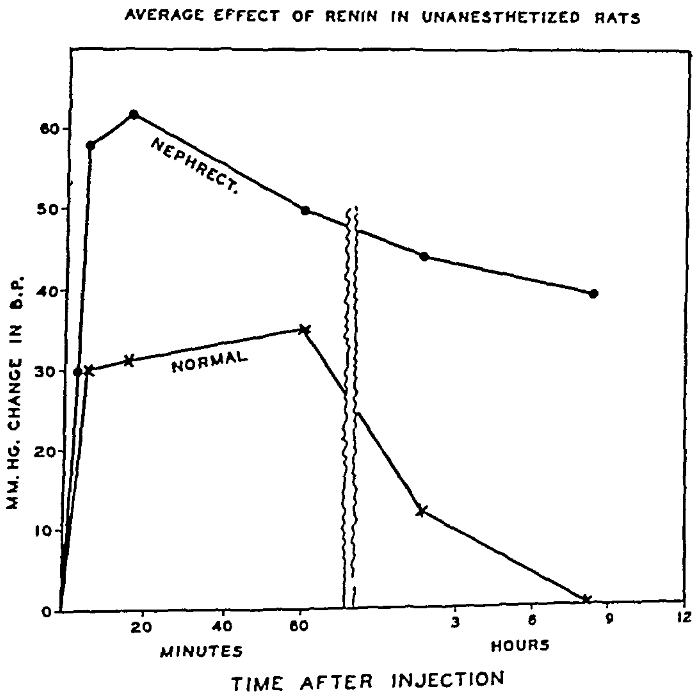

Fig. 2.—Composite curves, showing the average blood pressure change of all normal and all nephrectomized rats after intraperitoneal injection of 1 c.c. of renin. The base line represents the average pressure before injection. The first point is an average of all blood pressure readings from four to seven minutes after injection; the second, ten to twenty minutes; the third, fifty to sixty minutes; the fourth, two to three hours; and the fifth, four to twelve hours.

SUMMARY

1. A study has been made of the effect of nephrectomy on the response to renin in unanesthetized rats.

2. Nephrectomized rats have been found to be abnormally sensitive to the pressor effects of renin, both as to degree and duration.

3. The intact kidney, from which the pressor substance, renin, is extracted, appears to possess the property, in vivo, of counteracting, in some manner, the effect of this same substance when it is artificially injected.

4. The method of extracting renin from the kidneys has been modified in a manner which seems to eliminate the initial depressor effect.

5. Unanesthetized rats have proved to be useful subjects for the study of the pressor effects of renin.

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THE USE OF "EXERCISE TESTS" IN CONNECTION WITH VENOUS PRESSURE MEASUREMENTS FOR THE DETECTION OF VENOUS OBSTRUCTION IN THE UPPER AND LOWER EXTREMITIES

A Preliminary Report

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MEASUREMENT of the pressure in the peripheral veins is generally recognized as a diagnostic procedure of substantial value in a variety of diseases. The finding of an elevated pressure in the antecubital veins is sometimes the only means of detecting with certainty the presence of congestive heart failure. In obvious cases, in which it would be superfluous as a diagnostic test, it may still be used to advantage in gauging the severity of the heart failure and in following its progress. Measurement of the venous pressure is similarly useful in cases of acute and chronic cardiac compression. Comparisons of the pressures in the veins of the four extremities are helpful in the localization and diagnosis of arteriovenous fistula and of diseases causing partial or complete occlusion of one of the venae cavae or its branches. Venous pressure measurements are useful in the diagnosis of mediastinal lesions (especially mediastinal tumor), pleural and pulmonary diseases which alter the intrapleural pressure, intra-abdominal tumors, cirrhosis of the liver, ascites, and localized obstruction of the peripheral veins. In view of the fact that local lesions of the peripheral veins are so common (especially such conditions as thrombosis, phlebitis, and a varicose state), it is somewhat surprising that the applicability of venous pressure measurements to the diagnosis and study of these lesions has received comparatively little mention in the literature.

The term "venous pressure" requires some definition in order that it may be perfectly understood. It is used most commonly in connection with measurements which are referred to the level of the right auricle as a zero point for hydrostatic pressure and are obtained with the patient in a standard supine position. It has been suggested[1] that when the position of the right auricle is taken into consideration, the venous pressure be designated as "general" venous pressure. The term "local" venous pressure is reserved for measurements which are made without reference to the position of the heart or the posture of the patient, and with the zero point at the level of the vein that is being studied. In this paper, the term "venous" pressure will be considered to mean "general" venous pressure, unless otherwise stated.

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There are three principal methods for estimating the peripheral venous pressure. The first of these consists in direct inspection and palpation of the vein. The second measures the pressure necessary to produce collapse of the vein or to prevent its filling. This is the so-called indirect method. The third measures the pressure exerted through a needle inserted into the vein in terms of the height of a column of liquid sustained by this pressure. This is the so-called direct method. The first two of these three methods are inaccurate and inadequate in several ways which need not be enumerated here. The direct method, on the other hand, is not only reasonably accurate when carefully used, but is entirely adequate to meet practically all requirements for measurement of the venous pressure.

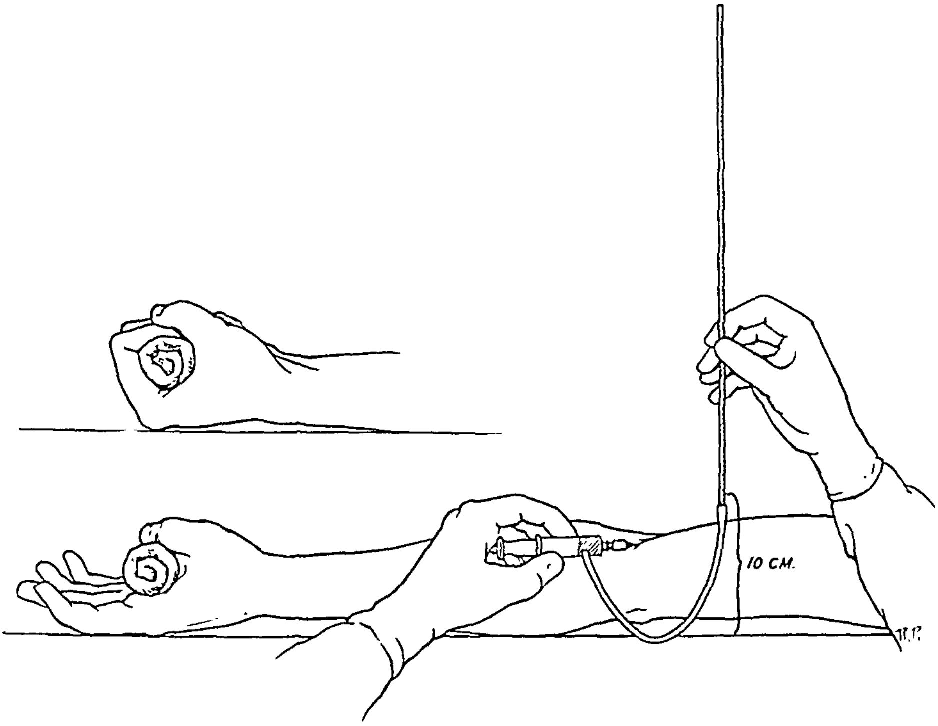

Fig. 1.—Apparatus and "exercise test" for studying antecubital venous pressure.

With certain exceptions, to be noted, the apparatus (Fig. 1) devised by Griffith, Chamberlain, and Kitchell[2] was used in these studies for measurement of the venous pressure in the antecubital or femoral vein. The apparatus consists of a 19-gauge needle and a 2 c.c. syringe with a sidearm to which a calibrated glass measuring tube of 4 mm. bore is connected by means of suitable rubber tubing. The other end of the glass tube is connected by means of another short piece of rubber tubing to a glass reservoir. The entire apparatus can be sterilized by boiling. Physiologic salt solution is placed in the reservoir and allowed to fill the entire apparatus, which is then ready to use. The patient is allowed to rest in the supine position for from fifteen to thirty minutes before measurement of his venous pressure is attempted. The arm in which the measurement is to be made is abducted to an angle of about 45°, and the needle is introduced into one of the veins of the antecubital fossa. The plunger of the syringe is drawn back, allowing saline to run through the sidearm into the syringe, and thence into the vein. Next, the reservoir is detached from the apparatus, and the zero point of the calibrated tube is placed

10 cm. above the skin of the patient's back. This reference point has been shown by Lyons, Kennedy, and Burwell[1] to be approximately level with the right auricle. The level of the column of saline falls, fluctuating somewhat with respiration, and stops at a point which indicates the height of the venous pressure in terms of millimeters of saline. Using this technique, it has been found that normal persons have a venous pressure of from 50 to 150 mm. This constitutes the basal venous pressure.

In some cases of mild or potential right ventricular failure, the venous pressure may be within normal limits. In such cases, special tests have been devised for verifying the existence of the heart failure. For example, raising the legs while the trunk remains horizontal has been shown to produce a rise of 30 mm., or more, in the venous pressure of patients with heart failure, but this maneuver has little or no influence on the venous pressure of normal persons.[3] Similar effects are obtained when the right upper quadrant of the abdomen is compressed for about a minute.[4] Also, it has been suggested[5] that the effect of exercise on venous pressure might be helpful in the detection of mild or incipient heart failure. All of these special tests record the venous pressure under practically basal conditions. As far as we have been able to discover, there has been no report of a diagnostic test which employs venous pressure measurements *during* exercise of the patient or a portion of his body.

The usefulness of venous pressure measurements in the differentiation of edema caused by lymphatic obstruction from that caused by venous obstruction was clearly shown by one of us in a study of cases of edema of the arm following radical mastectomy.[6] However, in some of these cases venograms revealed obstruction of the main venous channels and what seemed to be an inadequate collateral circulation, but the basal venous pressure in the edematous extremity was within normal limits. Moreover, there was an increase in the edema when the patient was allowed full use of the arm. In other cases in which there was no edema as long as the arm was kept at rest, edema would appear after vigorous exercise for a day. Therefore, it seemed obvious in these cases that the collateral circulation was adequate for the venous return while the arm was at rest, but not for the greatly increased return required by exercise. Similar observations were made in cases of traumatic thrombosis of the axillary and subclavian veins.

Judging from these studies, measurement of the basal venous pressure was misleading because it seemed to indicate that there was no venous obstruction, although the latter was actually demonstrated by means of the venogram, the obvious enlargement of collateral veins, and the presence of edema. Furthermore, it is important to recognize that, in these cases, exercise of the affected arm was the factor which demonstrated the inadequacy of the collateral circulation and determined the degree of venous obstruction. As we have already said, provision for the venous return may be adequate with the arm at rest,

but seriously inadequate during exercise. Therefore, a method which would reveal the changes in venous pressure during exercise of the affected arm would indicate more accurately the presence and degree of venous obstruction. Measurement of the venous pressure during exercise would be more valuable than a measurement obtained in the usual way immediately after exercise, because in some cases of peripheral venous obstruction the effects of exercise on the venous pressure might be quite transitory. With these facts in view, we have devised the simple procedures which are to be described in this paper.

THE "EXERCISE TEST" IN THE UPPER EXTREMITY

Method.—The pressure in the antecubital vein is measured by the method described above. With the venous pressure apparatus still in use, a roll of bandage is placed in the patient's hand on the same side on which the measurement is being taken. The patient is told to close and open his hand, squeezing the bandage tightly with each contraction and relaxing completely when the hand is open (Fig. 1). This is continued for one minute, during which the patient usually will have clenched his fist from thirty to forty times. It is important to instruct the patient to restrict his exertion to the arm, and to try to continue breathing regularly and evenly.

We have found in some cases of obstruction of the axillary and subclavian veins that the venous pressure may rise so high during the exercise test that it cannot be recorded conveniently with the saline manometer. In such cases it is possible to substitute a mercury manometer by means of a three-way stopcock (Fig. 2). In making readings during the exercise test, if it is found that the venous pressure is rising too high for measurement by the saline manometer, the lever of the stopcock is turned so that the pressure is measured in millimeters of mercury while the exercise continues. Later this measurement can be translated easily into millimeters of saline.

Clinical Application.—When this exercise test is applied to normal persons, the venous pressure usually rises a few millimeters above the basal level. We have not observed a rise of more than 10 mm. of saline in any normal subject, and, at the conclusion of the exercise, the pressure returns very promptly to, or slightly below, the basal level. In some cases no rise can be demonstrated, and the pressure may even fall slightly during the exercise. Prolongation of the exercise does not materially influence the results.

In cases of congestive heart failure the venous pressure may be initially high, but the effect of the exercise test is the same as in normal subjects. Apparently, the type of venous obstruction that occurs in heart failure has no influence on the exercise test. This observation seems to us to be of some importance. As will be seen, it may be an additional means of differential diagnosis in cases of edema in which the venous pressure is elevated.

The effects of the exercise test are quite different in cases of local obstruction of the axillary or subclavian vein. In most of the cases which we have had the opportunity to observe, venographic studies have been employed to confirm the presence and location of the obstruction. Whether or not the venous pressure is initially high in the affected arm.

it rises steadily during the exercise test. The pressure may reach a peak within the usual one-minute period of exercise, or may not attain its maximum level unless the exercise is continued for several minutes, or even longer. During the test, when the patient's hand is relaxed, the pressure sometimes continues to rise, or it may remain unchanged until the next manual contraction. The rise of venous pressure in every case of this type that we have studied has exceeded 50 mm. of saline; in one case the rise was 962 mm.

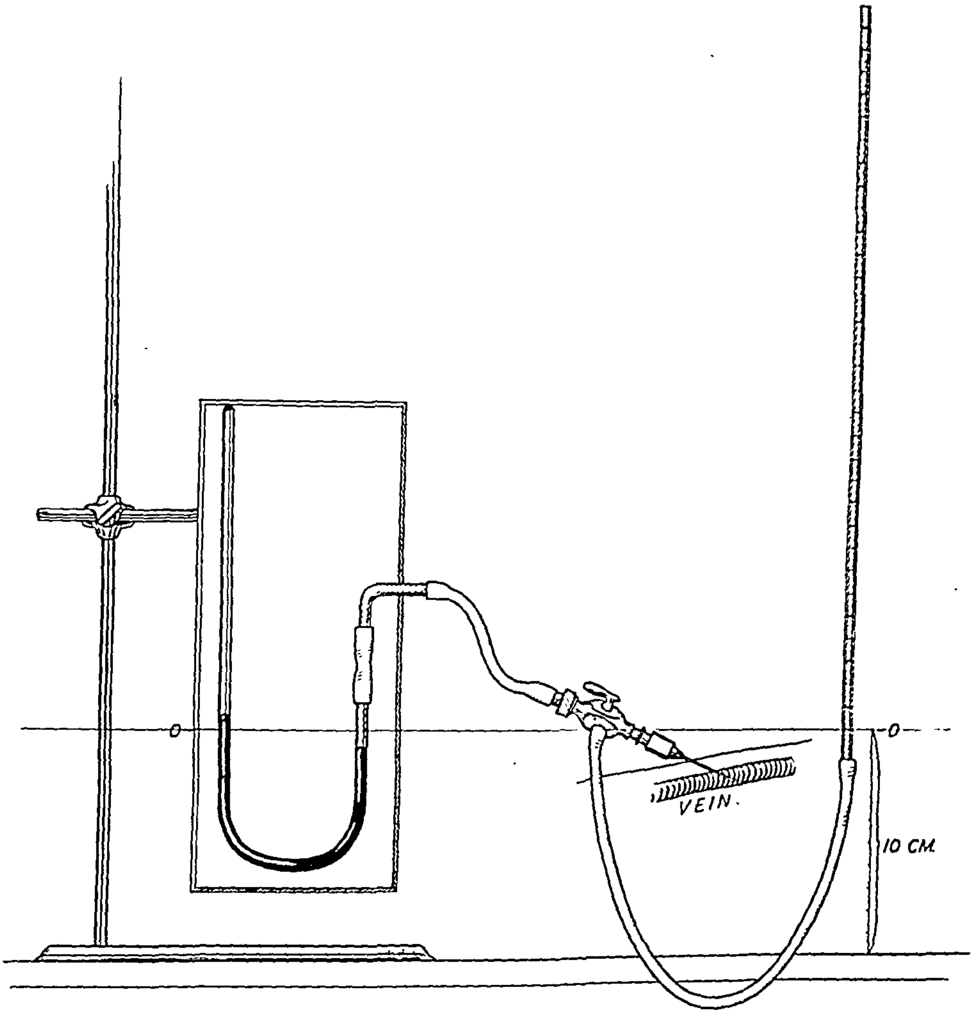

Fig. 2.—Apparatus for substituting a mercury for a saline manometer during measurement of venous pressure.

Whereas, in normal subjects, completion of the exercise test is followed by a prompt return of the venous pressure to, or below, its initial level, in the cases of venous obstruction the fall is slower, and the pressure may not reach the initial level for several minutes. The rapidity of the fall apparently depends upon the degree of venous occlusion and the extent of the collateral circulation. When the obstruction is severe and collateral vessels are few, the venous pressure may remain above the initial level for several minutes. When there are numerous collateral vessels, the fall is more rapid, but the return to the original level is never so prompt as in normal persons.

The sensitivity of the exercise test and its value in diagnosis are demonstrated in the reports of the following cases.

REPORT OF CASES

CASE 1.—The patient was a 65-year-old white woman who was receiving treatment for congestive heart failure secondary to coronary arteriosclerosis. She developed tenderness and prominence of the veins of the left upper extremity and slight edema of the left hand. These changes were believed to be caused by localized thrombophlebitis of the axillary vein. The pressure in the antecubital veins was 265 mm. of saline on the left, and 235 mm. on the right. During performance of the exercise test for one minute, the pressure rose to 360 mm. on the left and 250 mm. on the right. On cessation of exercise, the pressure returned to its original levels within about thirty seconds. These results were interpreted as confirmatory of the diagnosis of heart failure, with localized venous obstruction. One week after these original measurements were made, the patient had improved considerably. The tenderness of the veins of the left arm and the edema of the hand had disappeared. At this time the pressure was initially the same in the antecubital veins of the two arms. However, the exercise test produced a response almost identical with that obtained on the first occasion. The fact that the venous pressure was initially the same in the two arms indicated that there had been some lessening of the localized venous obstruction, but the exercise test showed that the obstruction had not disappeared entirely.

CASE 2.—This patient was a 65-year-old negress who had had a radical mastectomy, followed by deep roentgen therapy, for carcinoma of the left breast. Edema of the left upper extremity appeared several weeks after the operation, and it had persisted during the ensuing three years. The edema was aggravated by activity, especially by work requiring much use of the arm, and was relieved to a large extent by rest. Examination three years after the mastectomy was performed showed that the left upper extremity was about twice the thickness of the right, and that this enlargement was caused by edema. There was a large, deeply contracted scar in the left axillary region. The causal relationship of this scar to the edema seemed obvious. The basal venous pressure was 130 mm. of saline in the left, and 100 mm. of saline in the right, antecubital vein. During the exercise test the pressure on the left side rose so high that it was necessary to utilize the mercury manometer in order to measure it. When the necessary calculation had been made, it was found that the pressure had risen to 962 mm. of saline after exercise for one minute. The return of the pressure to its initial level was delayed; one minute after stopping the exercise it was still 182 mm. of saline (Fig. 3). The exercise test had practically no effect upon the venous pressure in the right arm.

In this case, basal venous pressure measurements were of little value in the endeavor to prove that the edema of the left arm was caused by venous obstruction. However, the exercise test clearly substantiated this impression, which was further verified by venography.

CASE 3.—The patient, a 46-year-old negro, was admitted to Gallinger Municipal Hospital July 13, 1939. He complained only of swelling of the face, which had been present for ten days; his history was otherwise irrelevant except for the vague possibility that he might have had syphilis. The only important abnormalities were edema of the face and left upper extremity, dilatation of the veins of the arms and upper part of the thorax, and a strongly positive blood Kahn reaction. The suspicion that he might have a mediastinal tumor was not confirmed by roentgenologic examination, which showed only dilatation of the superior vena cava. The pressure in the antecubital veins was 510 mm. of saline on the left, and 500 mm. on the right. Compression of the right upper quadrant of the abdomen caused a fall on both sides. The femoral venous pressure was 70 mm. of saline. During the exercise test the venous

pressure rose to 590 mm. in both arms. After exercise was stopped, the pressure returned very slowly to its original level; it was still somewhat elevated at the end of three minutes. These observations were thought to prove beyond doubt that the superior vena cava was obstructed, but that the flow of blood from the inferior vena cava was unimpeded. Intensive antisyphilitic treatment with neoarsphenamine and potassium iodide was started on July 22, and by the middle of August all of the edema had disappeared. On August 8, the venous pressure in the right arm was 340 mm. During the exercise test it rose to 500 mm., and, when the exercise was continued for three minutes, it reached 615 mm. On August 31, the pressure in the antecubital veins was 320 mm. on the left, and 330 mm. on the right. The pressure rose to 520 mm. during the exercise test, but returned to its initial level within two minutes after exercise was stopped (Fig. 4). The patient was discharged from the hospital soon after the last measurements were made.

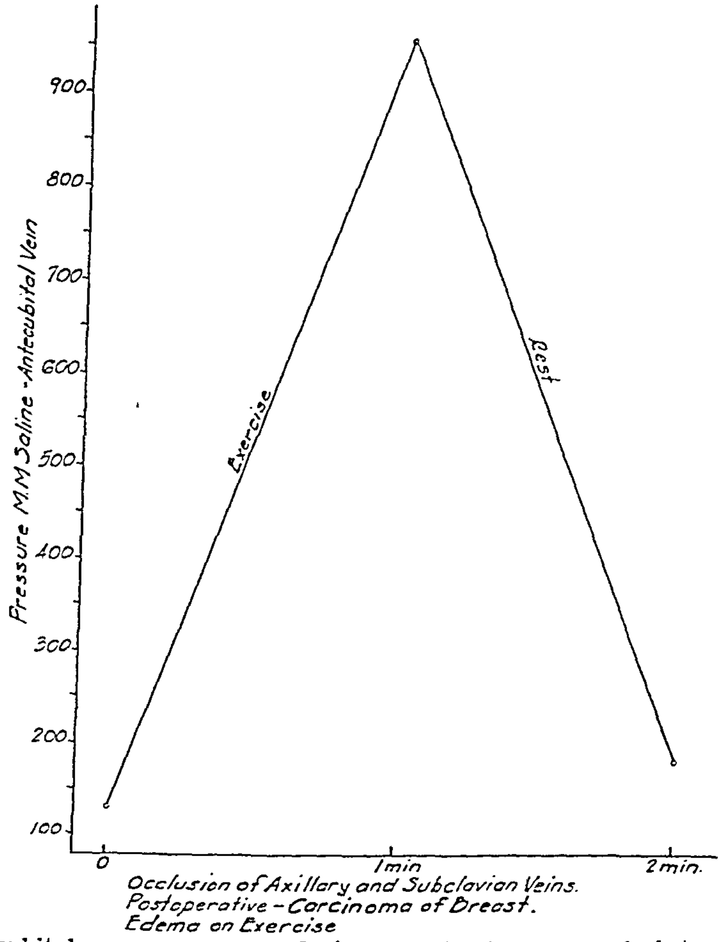

Fig. 3.—Antecubital venous pressure during exercise in a case of obstruction of the axillary and subclavian veins (Case 2).

In this case, obstruction of the superior vena cava was apparently ameliorated to some extent by antisyphilitic treatment. The venous pressure measurements, including those made during the exercise test, were a means of confirming the diagnosis and of demonstrating objectively that the patient's improvement was the result of lessening of the venous obstruction.

Case 4.—This patient was a 39-year-old white man who had been examined at the Georgetown University Hospital in October, 1939, at which time a diagnosis of constrictive pericarditis, with calcification of the pericardium, was made. Subsequently, he was sent to Dr. Claude S. Beck, at Cleveland, for operative treatment of the cardiac compression. The initial venous pressure was 290 mm. of saline in the right antecubital vein, and 295 mm. in the left. During the exercise

test the pressure rose to 340 mm. on the right side, and 345 mm. on the left. The time required for the pressure to return to its initial levels was 3¾ minutes in both arms.

This case demonstrated that chronic cardiac compression alters antecubital venous pressure in the same way as localized venous obstruction. The exercise test in such cases should serve as an additional means of differentiation from congestive heart failure.

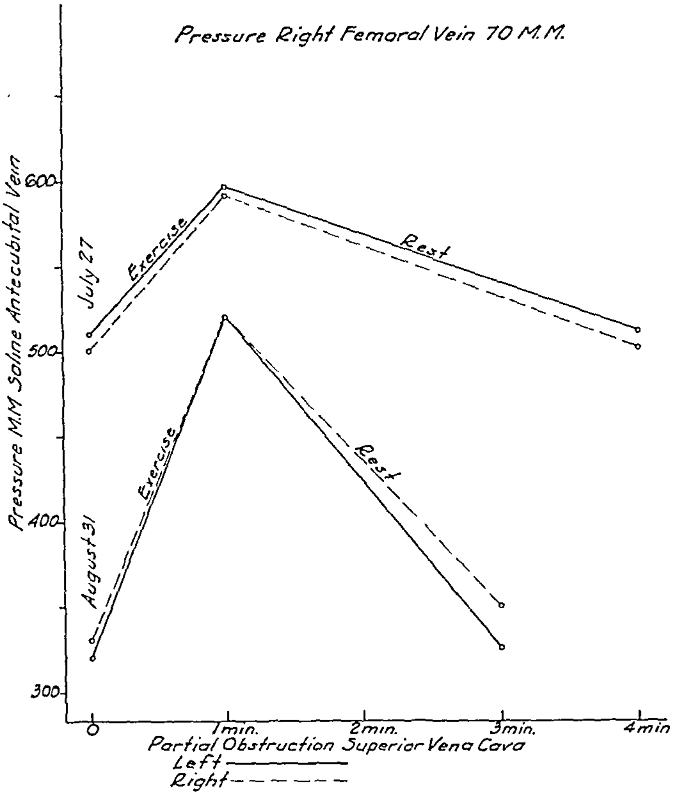

Fig. 4.—Effect of exercise on the antecubital venous pressure in a case of partial occlusion of the superior vena cava. Note the rapid rise in the pressure during exercise, and the gradual fall during the rest period (Case 3).

THE "EXERCISE TEST" IN THE LOWER EXTREMITY

There have been comparatively few clinical measurements of venous pressure in the lower extremities. The reason is that such measurements are most commonly made in cases of heart failure, and in this condition the antecubital vein is the most satisfactory one to use. Estimation of the pressure in the femoral or saphenous vein is recommended in the study of arteriovenous fistula of the lower extremity,[7] and to help detect obstruction of one of the venae cavae without obstruction of the other.[8] In the latter case, it is necessary to compare the pressure in the antecubital vein with that in the femoral.

Measurement of the femoral venous pressure is made with the same apparatus and technique which are used for the upper extremity, except that a tourniquet is not needed. The needle can easily be introduced through the skin into the femoral vein at a point about 1 inch

distal to the inguinal ligament, just medial to the femoral artery. The angle at which the needle is introduced will vary, depending on whether the vein is superficial or deep. This method has found practically no application in the study and diagnosis of localized venous obstruction in the lower extremity.

The symptoms and signs of obstruction of the iliac and femoral veins are often clear-cut and easily recognized. However, it may be difficult to be sure whether or not there is slight obstruction, especially when clinical evidence of phlebitis or venous collateral circulation is lacking. Similarly, in cases of unilateral or bilateral edema of the lower extremities, it may be difficult to discover the pathogenesis of the edema. Measurement of the pressure in the femoral vein, or in one of the superficial veins of the leg, with the patient supine, may be of no assistance in such cases, and the results may even be misleading. Just as in the upper extremity, the venous pressure under relatively basal conditions may not be altered by partial obstruction of the veins. This is especially true in conditions in which the obstruction does not become entirely effective until the patient assumes the upright position, as, for example, when there is compression of the pelvic veins by a tumor. Moreover, measuring the venous pressure in the leg or thigh while the patient is standing is usually not helpful in the diagnosis of venous obstruction because such pressures vary widely in normal persons, and because only the "local" venous pressure can be measured in this way. There is no way to express such a measurement in terms which take into consideration the position of the right auricle as a reference point. However, a record of the changes which take place in the "local" venous pressure of the lower extremity during exercise in the upright position is useful in the detection of venous obstruction. This kind of record can be obtained by using the popliteal vein.

The popliteal vein is formed by the junction of the anterior and posterior tibial veins at the lower border of the popliteus muscle. It receives the lesser saphenous vein and a few minor tributaries. It is about the size of the axillary vein, and is, of course, fully distended when one stands on one's feet. It can be easily punctured for venous pressure studies if careful attention is paid to certain anatomic landmarks. The vein lies superficial to the popliteal artery and medial to the tibial nerve. The upper third of the vein is covered by the semimembranosus and semitendinosus muscles, and the lower third by the gastrocnemius muscle. It is most superficial in the middle third, where it is covered only by the deep fascia, subcutaneous tissue, and skin. This part of the vein is most accessible for venipuncture, and particularly for performance of the exercise test, because, when a needle is inserted into the vein at this point, it will not be affected by contraction of the muscles (Fig. 5).

Method.—The apparatus for measurement of the popliteal venous pressure consists of a mercury U-tube manometer, one arm of which is straight, and the other

arm bent at an angle to facilitate attachment of a piece of rubber tubing. A millimeter scale is affixed beside the straight arm for the purpose of recording pressure. Readings from this scale must be doubled, of course, in order to obtain the actual pressure in millimeters of mercury. The other arm is filled completely, from the surface of the column of mercury to its tip, with 2.5 per cent sodium citrate solution. The height of the column of mercury beside the millimeter scale is noted. Next, a sterile length of rubber catheter, with a needle adaptor in one end, is filled completely, by means of a sterile 5 c.c. syringe, with sterile 2.5 per cent sodium citrate solution. This tubing is clamped with a small hemostat, and its free end is then slipped on the designated arm of the manometer, care being taken to exclude air bubbles from the system. The manometer is adjusted on its supporting stand in such a way that the zero level of the column of mercury is on a plane with the point at which the venipuncture is to be made. This adjustment is accomplished by means of a carpenter's level.

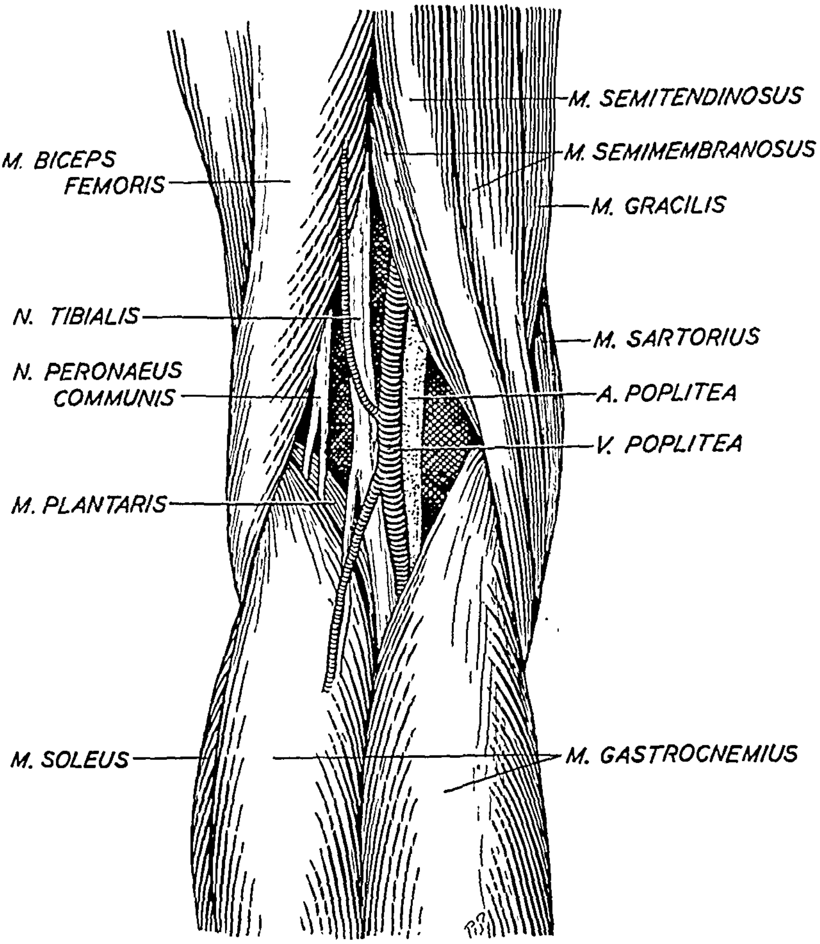

Fig. 5.—Anatomic relations of the popliteal vein.

The patient is instructed in the procedure of the test and is shown how to perform the exercise. He stands erect, with feet slightly apart, on a smooth table set against the wall, where supports are provided for his hands. The lower halves of the thighs, and the legs, are exposed; the shoes and stockings are removed. Standing behind the patient, the operator palpates the lower border of the patella with his index finger, and locates with the thumb of the same hand a point on the same level, just medial to the lateral head of the gastrocnemius and the plantaris muscles. After appropriate sterilization of the skin, a wheal is produced at this point with

The column of mercury in the manometer will quickly come to a level which indicates the local pressure in the vein. The height of this level is recorded as the initial venous pressure. The patient then begins the exercise, which consists in rising on his toes repeatedly (twenty to thirty times) for one minute (Fig. 6). It is important that he use the hand supports on the wall only for the purpose of steadying himself, and not as a means of assisting in the exertion, that he breathe regularly during the exercise, and that he relax the muscles of his legs each time his heels are lowered to the surface of the table. During the test it is necessary for the operator to support the rubber tubing of the apparatus with his hand, in order to keep the needle horizontal and prevent it from slipping. The changes in venous pressure during exercise are recorded, and the pressure is observed for a short time after exercise has ceased. The needle is then withdrawn, and firm pressure is applied for about a minute at the site of venipuncture. The patient is required to walk around the room for a few minutes at the conclusion of the test in order to minimize the likelihood of venous thrombosis.

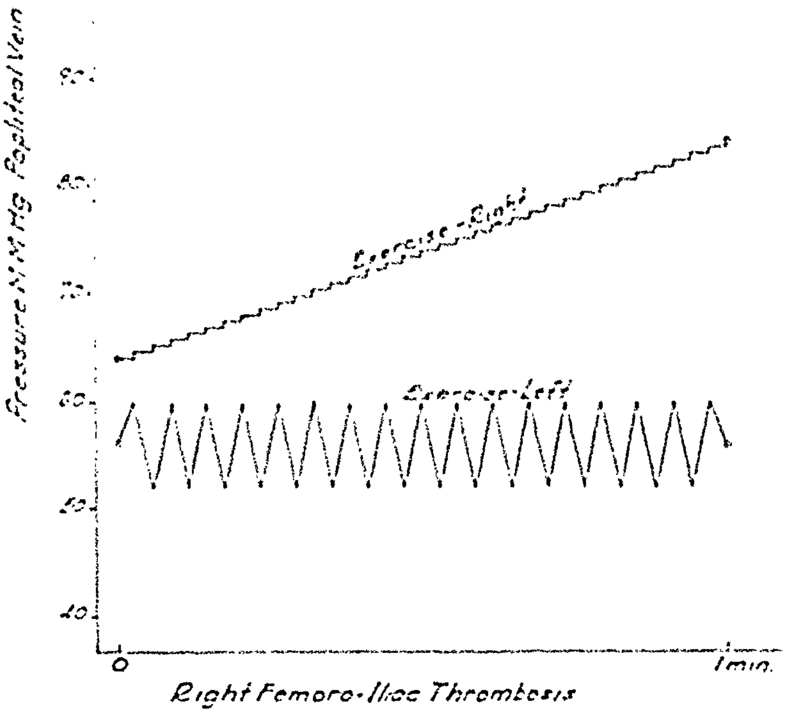

Fig. 7.—Steady rise in popliteal venous pressure during exercise in a case of obstruction of the right iliac and femoral veins. Note the fluctuations in the popliteal pressure in the normal lower extremity (Case 5).

Clinical Application.—In the absence of obstruction of the veins of the lower extremity, the exercise test has little effect upon the local pressure in the popliteal vein. Usually, the column of mercury will fluctuate slightly, rising each time the patient moves up on his toes, and falling when he lowers himself. The average range of this fluctuation is about 4 mm. above and below the initial pressure. In some cases the exercise produces only a slight fall in the venous pressure.

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GALVANOMETRIC POTENTIALS OF THE EXTREMITIES AND OF THE THORAX IN CONGENITAL DEXTROCARDIA

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IN PRECORDIAL electrocardiograms of normal subjects it has been shown that the deflection analogous to the intrinsic deflection of direct leads[1] occurs, on the average, 0.16 sec. later in leads from the left side of the precordium than in leads from the right side.[2, 3] This has been interpreted to mean that excitation reaches the epicardial surface of the anterior wall of the right ventricle earlier, on the whole, than it reaches the corresponding surface of the left ventricle. It has been concluded, largely from experimental observations,[4] that the difference is due principally to the greater thickness of the left ventricle in normal adults. Further support for the truth of this assumption can be obtained in several ways. One of the simplest is to measure the time of the intrinsicoid deflection[1] in the precordial electrocardiograms of subjects who are normal in all respects except that the position of their cardiac chambers is reversed. The desired conditions are found in cases of uncomplicated, congenital dextrocardia.

METHODS

Nine subjects were studied, but four were excluded because the dextrocardia was complicated by rheumatic, hypertensive, or arteriosclerotic heart disease. Of the remaining five, all of whom had complete situs inversus viscerum, four were women whose ages ranged from 20 to 32 years, and the other was a boy, aged 12 years. One of the women (Case 4) was in the fifth month of a uterine pregnancy. None of the subjects displayed any clinical, radiologic, or electrocardiographic evidence of cardiac disease, other than dextrocardia.

Two string galvanometers, arranged to record simultaneously on the same film, were employed.[5] The first was connected to the balanced plate circuit of a single-stage vacuum-tube amplifier. It was used to record the following (upper curve in each illustration): standard Leads I, II, and III; the potential variations of the right arm (V_R), of the left arm (V_L), and the left leg (V_F); the potential variations of nine points on the thorax, namely, V_1, fifth rib at the right sternal edge; V_2, fifth rib at the left sternal edge; V_3, fifth intercostal space in the left parasternal line; V_4, fifth intercostal space in the left midclavicular line; V_5, sixth rib in the left anterior axillary line; V_E, tip of the ensiform process; V_6,* fifth intercostal space in the right parasternal line; V_7, fifth intercostal space in the right midclavicular line; V_8, sixth rib in the right anterior axillary line. The string sensitivity when the standard leads and the extremity potentials were recorded was normal (1 cm. = 1 mv.); when the thoracic potentials were recorded it was half normal (1 cm. = 2 mv.). The extremity and thoracic potentials were obtained by the method of Wilson, Johnston, Macleod, and Barker.[6] In Case 1 the connections to the galvanometer were so made that positivity of the exploring

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*It is to be noted that Lead V_6 in this instance is not the lead of this designation described in the Standardization of Precordial Leads.[7]

electrode resulted in a downward movement of the string shadow. They were labeled, therefore, as if they were upside down (Figs. 1 and 2), in accordance

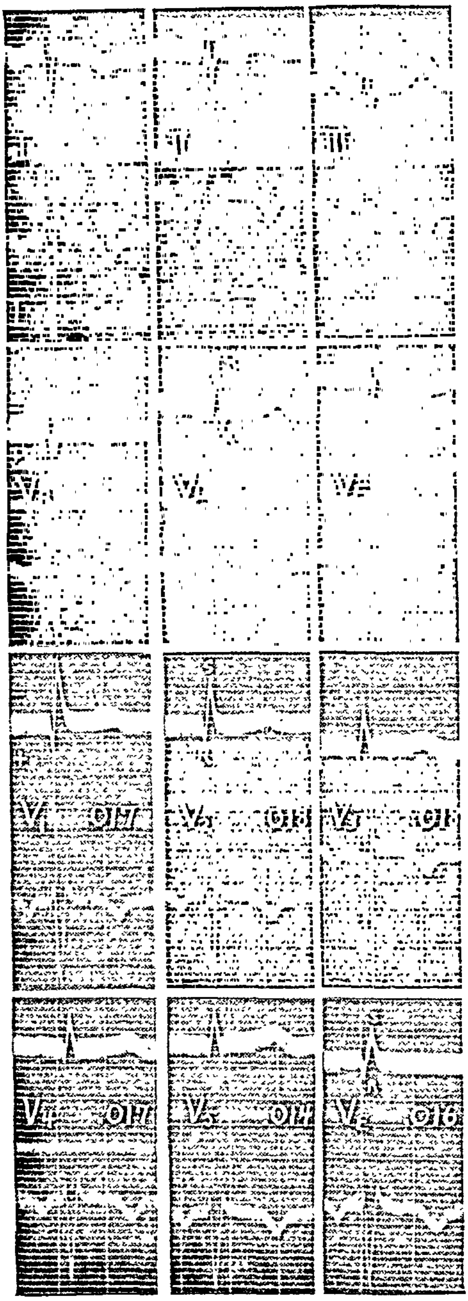

Fig. 1.—Standard electrocardiograms, extremity potentials, and potentials of the left border of the precordium and left side of the chest, in Case 1. The upper curve in each illustration shows, I, standard Lead I; II. standard Lead II; III, standard Lead III; V_R, V_L, and V_F are the potential variations of the right arm, the left arm, and the left leg, respectively. These six curves were taken with the string at normal sensitivity (1 cm. = 1 mv.). The next six curves, which were taken with the string at half normal sensitivity (1 cm. = 2 mv.), represent the potential variations of the following thoracic points: V_1, fifth rib, right sternal edge; V_2, fifth rib, left sternal edge; V_3, fifth intercostal space, halfway between the left sternal edge and the left midclavicular line; V_4, fifth intercostal space in the left midclavicular line; V_5, sixth rib in the left anterior axillary line; V_E, tip of the ensiform process. The lower curve in each illustration is standard Lead I, taken with the string at normal sensitivity. The figure on each record is the time in seconds between the beginning of QRS in standard Lead I and the intrinsicoid (RS) deflection of the chest lead. The time intervals are 0.2 second.

with the recommendations of the Committee on Precordial Leads of the American Heart Association.[7] In the remaining four cases the potentials were recorded as recommended by the Committee.

The second galvanometer was used, in the usual way, to record standard Lead I at normal string sensitivity (lower curve in illustrations). The thoracic electrode was of German silver; it was circular, and measured 1.5 cm. in diameter. The electrodes on the extremities were rectangular plates of German silver, 5 cm. by 3.5 cm. Contact between the electrodes and the body was made with electrode jelly.*

In two cases (Nos. 1 and 3), small lead markers were placed on the points from which chest leads had previously been made, and teleroentgenograms were taken. In one case, large breasts prevented accurate recording of any but the three mid-thoracic leads (Fig. 3); in the other, a young boy, the relationship of the markers to the cardiac silhouette was similar to that shown in Fig. 3.

The time between the beginning of the intrinsicoid (RS) deflection of the thoracic leads and the beginning of QRS in Lead I was measured with a comparator designed by Capt. Elliott.*

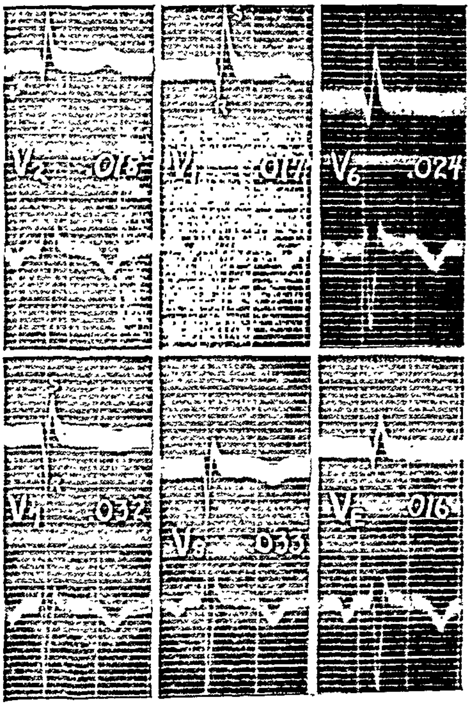

Fig. 2.—The potential variations of the precordium in Case 1. V_1, V_2, and V_E are identical with similarly designated curves in Fig. 1. The other three curves show the potential variations of the following points: V_6, fifth intercostal space, halfway between the right sternal edge and the right midclavicular line; V_7, fifth intercostal space in the right midclavicular line; V_8, sixth rib in the right anterior axillary line. The curves have been arranged in the order shown for the purpose of emphasizing their mirror-image similarity to those obtained from the left side of the chest of a normal subject. Time intervals and lower records as in Fig. 1.

OBSERVATIONS

The standard electrocardiograms were normal in all respects, except for complete inversion of Lead I. The minimum, maximum, and mean voltages of the ventricular deflections in the standard and special electrocardiograms are given in Table I.

The potential variations of the left arm (V_L) were principally negative (Fig. 1). A positive deflection (R wave), if present, was small.

*Cambridge Instrument Co.

TABLE I

SIZE OF THE VENTRICULAR DEFLECTIONS IN THE STANDARD AND SPECIAL LEADS IN 5 CASES OF DEXTROCARDIA (MEASUREMENTS IN TENTHS OF A MILLIVOLT)

LEAD	Q			R			S			T			RS*		
	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN	MIN.	MAX.	MEAN
I	0	3.0	0.60	1.0	1.5	1.30	0	12.0	8.10	-3.0	-2.0	-2.40	4.5	13.5	10.40
II	0	1.0	0.20	1.5	7.0	3.20	0	7.0	3.60	0	2.0	0.90	4.0	8.5	7.00
III	0	0.5	0.20	3.0	10.0	7.80	0	2.5	1.10	2.0	5.0	2.90	4.0	12.5	9.00
V_R	0	1.0	0.36	1.0	5.0	2.90	0	4.0	1.00	0	1.0	0.70	2.0	6.0	3.90
V_L	0	7.0	2.60	0	1.0	0.60	0	5.5	2.10	-2.5	-1.0	-1.60	3.5	8.0	5.30
V_F	0	0.5	0.10	0.5	5.0	2.10	0	3.0	1.20	0.5	2.0	1.10	1.5	4.0	3.40
V_1	0	0	0	5.0	13.0	8.20	11.0	36.0	21.40	-1.0	2.0	0.30	18.0	49.0	27.60
V_2	0	0	0	2.5	7.0	4.50	6.0	24.0	13.40	-2.0	-0.5	-1.40	8.5	37.0	21.30
V_3	0	0	0	1.0	5.0	2.72	4.0	15.0	9.0	-3.0	-0.5	-1.70	5.0	20.0	11.72
V_4	0	0	0	0.5	3.5	2.00	2.0	8.5	6.70	-3.0	0	-1.60	2.5	12.0	8.70
V_5	0	0	0	0.5	2.0	1.20	0	8.0	4.80	-3.0	0	-1.20	0.5	9.5	6.00
V_E	0	1.0	0.20	3.0	6.0	4.10	2.0	16.0	9.40	0	0.5	0.20	5.0	22.0	13.50
V_6	0	0	0	6.0	13.0	9.0	5.0	18.0	11.80	0.5	4.0	2.70	11.0	31.0	20.80
V_7	0	1.0	0.30	8.0	38.0	17.20	4.0	8.0	6.30	2.0	6.0	4.40	16.0	43.5	23.50
V_8	0	2.0	0.80	8.0	22.0	14.60	0	5.5	2.50	2.0	7.0	4.40	11.0	22.0	17.10

*Or QR, depending on which is larger

The T wave was negative. The left arm was, as might be expected, electrically similar to the right arm in a normal subject.

The mean potential of the right arm during the inscription of QRS was negative, zero, or positive, depending upon whether the mean electrical axis* was deviated slightly, moderately, or markedly to the right. A reverse relationship was found between the mean potential of the left leg and the electrical axis (Table II).

TABLE II

THE ANGLE ALPHA IN FIVE CASES OF DEXTROCARDIA, ARRANGED TO SHOW THE EFFECT OF ITS INCREASE ON THE MEAN POTENTIAL OF THE RIGHT ARM (V_R) AND OF THE LEFT LEG (V_F) WHEN THE MANIFEST POTENTIAL, E, IS RELATIVELY CONSTANT. VALUES FOR E, V_R, AND V_F ARE GIVEN IN TENTHS OF A MILLIVOLT

CASE	ANGLE ALPHA	$E = \frac{e_1}{\cos a}$	LEAD V_R	LEAD V_F
5	+101°	10.3	-1	5
3	+143°	9.9	0	2
1	+156°	9.9	3	0
2	+183°	11.0	5	-1
4	+193°	7.2	4	0

TABLE III

TIME OF ONSET OF INTRINSICOID (RS) DEFLECTION IN CHEST LEADS, WITH REFERENCE TO THE EARLIEST VENTRICULAR DEFLECTION OF LEAD I IN FIVE CASES OF DEXTROCARDIA. AVERAGES OF THESE FIGURES IN NORMAL SUBJECTS ARE INCLUDED AT FOOT OF TABLE FOR COMPARISON

CASE	LEADS FROM RIGHT SIDE OF ANTERIOR THORAX			LEADS FROM MIDTHORAX ANTERIOR			LEADS FROM LEFT SIDE OF ANTERIOR THORAX		
	V_8	V_7	V_6	V_1	V_E	V_2	V_3	V_4	V_5
1	0.033	0.032	0.024	0.017	0.016	0.018	0.018	0.017	0.014
2	0.040	0.040	0.037	0.019	0.014	0.015	0.014	0.016	0.016
3	0.037	0.034	0.024	0.022	0.019	0.023	0.025	0.021	0.020
4	0.034	0.034	0.022	0.023	0.019	0.021	0.016	0.018	0.018
5	0.028	0.032	0.016	0.014	0.015	0.008	0.009	0.008	–
Means	0.0344	0.0344	0.0246	0.0190	0.0166	0.0170	0.0164	0.0160	0.0170
Means in normal subjects	0.0167*	0.0166*	0.0184*	0.0172	0.0249	0.0193	0.0314	0.0349	0.0326

*Means of 5 normal subjects. Remaining figures on this line represent the averages of 30 normal subjects.[3]

As the thorax was explored, all of the ventricular deflections changed in size, as shown in Table I. On the average, the R wave became taller as the exploring electrode was moved from the right side to the left side of the chest, and reached its maximum size in the lead from the right midclavicular line (V_7). The S wave was largest in the lead from the right sternal edge (V_2). It diminished in size as the distance between the right sternal edge and a lead on either side of it was increased. The same was true of the RS deflection, with the exception of Lead V_7, in which RS was slightly greater than in Lead V_6. In the

*The mean electrical axis was obtained by applying the method of Carter, Richter, and Greene[8] to the algebraic sum of QRS deflections in Leads I and III. "Mean electrical axis" was originally, and more accurately, determined from the area of the ventricular deflections.[9]

five cases, a Q wave was encountered once in Lead V_E, twice in Lead V_7, and three times in Lead V_8. The T wave was isoelectric or negative in leads from the left side or middle of the chest, and positive in leads from the right side.

The time of onset of excitation in the various precordial leads is shown in Table III. For comparison, the average values of these determinations in normal subjects are included on the lowest line. It is apparent that, in the anterior midthorax, excitation arrives, on the average, at approximately the same time in the normal subject as in the person with dextrocardia. In the latter, the time of arrival on the right side of the precordium is considerably later than on the left side, which is the reverse of what is found in the normal subject.[3] Significant

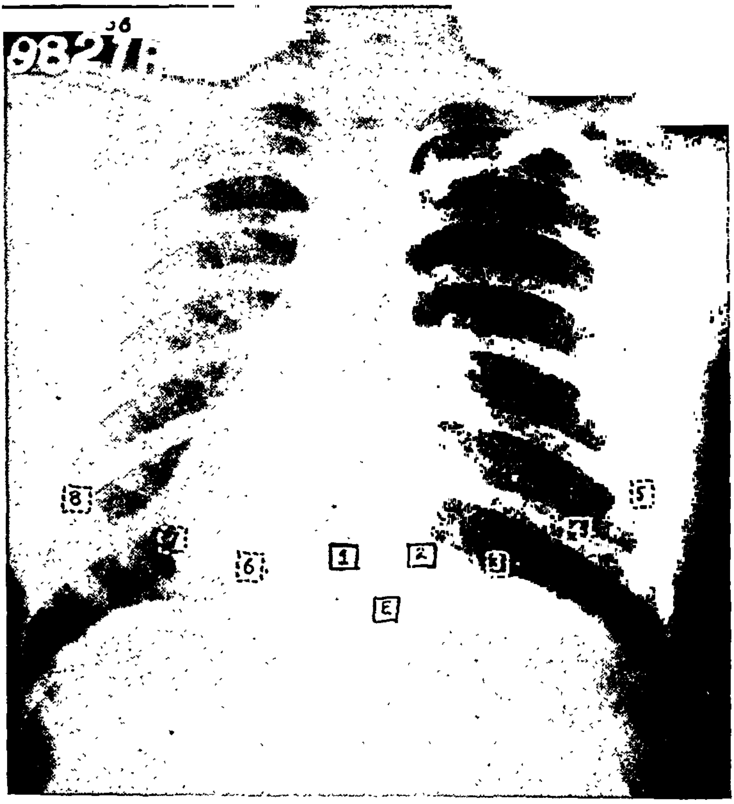

Fig. 3.—Teleroentgenogram in Case 1, showing the approximate location of the thoracic leads with respect to the cardiac silhouette. The relationship of points V_1, V_2, and V_E was ascertained by placing small lead markers on the chest before the roentgenogram was taken; these points are indicated by squares of solid lines. Other points could not be located accurately in this manner because of prominent breasts. The approximate location of each has been indicated by squares of dotted lines.

differences are noted between average values of Lead V_6 in cases of dextrocardia and the comparable Lead V_3 of the normal subject, and between the values for Lead V_E in the two groups. A large number of cases would probably reduce these differences. In cases of dextrocardia, the average onset of excitation in the first two leads (V_1 and V_2) was 0.0160 sec. earlier than the average onset in Leads V_7 and V_8. The comparable figure in normal subjects, which is the difference

between the average onset in the first two leads and the average onset in the fourth and fifth (V_4 and V_5) is 0.012 sec.

SUMMARY

The results indicate that the electrical field of the heart in cases of dextrocardia is, in effect, a mirror image of the electrical field in the normal subject. That excitation reaches the surface of the thorax near the left ventricle later than it reaches the surface of the thorax near the right ventricle, in the human subject, irrespective of the location of these chambers, may be attributed to factors other than the difference in the thickness of the ventricular walls. The one that comes to mind first is the variation in conductivity of the several components comprising the surrounding medium. At present, there is no direct way of measuring the effect of this on electrical phenomena in the human subject, but the fact that the intrinsicoid deflection is abnormally late in midthoracic leads (V_2, V_3, V_4) in cases of right ventricular hypertrophy and right bundle branch block[2,9,10] and in leads from the left side of the chest in cases of left ventricular hypertrophy and left bundle branch block[2,4] suggests that, however heterogeneous the conducting medium may be, it has no significant influence.

The author is grateful to Drs. Harry Gold and [illegible] of New York, and Drs. Harold [illegible], Jacob [illegible], and Samuel [illegible] of Newark, for permission to study their cases.

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THE TOXICITY OF DIGITALIS AND OUABAIN IN ANIMALS UNDER SODIUM THIOPENTOBARBITAL AND SODIUM PENTOBARBITAL ANESTHESIA*

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ROWE[1] considered dogs unsatisfactory for digitalis assay. Using morphine-ether anesthesia, Haskell, Copenhaver, Stone, and Yost[2] experimented upon seventy-six dogs in an effort to ascertain whether or not they are suitable for the bio-assay of digitalis. They found that the lethal dose varied from 76.3 to 241 mg. per kilogram of body weight, and, consequently, they decided that dogs were less satisfactory than cats for this work. The average lethal dose in their series was 141 mg. of digitalis per kilogram of body weight. The wide range of the lethal dose was to be accounted for, they believed, by variations in the size and the age of the animals used.

Additional studies on the standardization of digitalis, using dogs, were made by McGuigan and McGuigan,[3] who anesthetized the animals by injecting sodium pentobarbital in doses of 35 mg. per kilogram intraperitoneally. The tincture of digitalis was injected intravenously in doses of 0.1 c.c. per kilogram of body weight every five minutes until the animal died. Their tincture was prepared from U.S.P. reference powder, as directed in the United States Pharmacopoeia XI, and, consequently, they say that their tinctures were made to contain 0.1 gram of the international powder in each cubic centimeter. Twenty-one dogs were used, and the average lethal dose was found to be 123 mg. per kilogram. These results checked within 10 per cent of the actual strength of the drug when any two animals were compared. They also ascertained the amount of ouabain, per kilogram of body weight, which was necessary to kill the animals. The average lethal dose of ouabain was found to be 0.104 mg. (0.092 mg. of water-free ouabain) per kilogram of body weight.

That anesthetic doses of thiopentobarbital can cause temporary cardiac irregularities in experimental animals which are not similarly affected by pentobarbital has been reported by a number of observers.[4, 5] This cardiac arrhythmia could be made to disappear by lowering the arterial blood pressure by hemorrhage, and by the administration of such drugs as amyl nitrite, nitroglycerine, and the salts of acetylcholine, histamine, or quinidine. If this irregularity was absent during and immediately after administering anesthetic doses of thiopentobarbital intravenously, it could be induced by elevating the arterial blood pres-

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sure by eliminating the carotid sinus reflex, and by the intravenous injection of ouabain, tyramine, ephedrine, or pitressin. In a few instances, epinephrine also induced the irregularity.[6]

Since pentobarbital was the anesthetic used by McGuigan and McGuigan in their studies of the toxicity of digitalis, we thought that it would be interesting to perform similar experiments, with sodium thiopentobarbital (pentothal) as the anesthetic agent, and compare our results with theirs. Such experiments, we believe, are of importance, for both sodium thiopentobarbital and digitalis are used clinically.

METHOD

Forty-four dogs were used in this investigation; seventeen were under sodium pentobarbital anesthesia, and twenty-seven under sodium thiopentobarbital anesthesia. In one group of experiments ether anesthesia was used for the preliminary operative procedures, after which one or the other of the above-mentioned anesthetics was administered intravenously. In a second group of experiments sodium pentobarbital was injected intraperitoneally, and, in a third series of experiments, sodium thiopentobarbital was injected intravenously in anesthetic doses.

After the animal was anesthetized, the trachea was exposed and cannulated to permit freer breathing and the use of artificial respiration when needed. The right carotid artery was freed and cannulated for recording the arterial blood pressure with a mercury manometer. Heparin was used as the anticoagulant. A small area on the left hind leg, and another similar area on the right foreleg were shaved, and German silver electrodes were applied to these spots. These electrodes were connected to a "Sanborn" string galvanometer.* Lead II was used throughout, and the string tension was adjusted to give an excursion of 2 cm. for each mv. The resistance was 2000 ohms. A commercial paste was employed to reduce skin resistance and to insure better contact between the electrodes and the skin.

The right femoral vein was exposed for the intravenous administration of the drugs. In these experiments, after completion of the operative procedures, electrocardiograms and blood pressure records were taken simultaneously. In those experiments in which ether was used, it was discontinued at this point, and, as the anesthesia became lighter, 20 mg. per kilogram of either sodium thiopentobarbital or sodium pentobarbital were slowly injected intravenously. When thiopentobarbital was used, additional electrocardiograms were taken after its administration, and after each injection of digitalis or of ouabain.

In some experiments, an electrocardiogram was taken as soon as the animal was fastened to an animal board. After this, 20 mg. per kilogram of sodium thiopentobarbital were injected into the saphenous vein. If this amount of thiopentobarbital was insufficient to produce surgical anesthesia, additional amounts were injected. The operative procedures were performed under this anesthetic in these experiments. As the animal recovered from the initial dose of thiopentobarbital, the drug was again injected in doses of 3 to 10 mg. per kilogram, i.e., in doses just sufficient to maintain surgical anesthesia.

In the experiments in which sodium pentobarbital was employed as the anesthetic, the drug was injected intraperitoneally in doses of 35 mg. per kilogram. No electrocardiographic studies were made on these animals.

Two tinctures of digitalis were used. In four experiments the "Wellcome" tincture was employed, but for the thirty-two remaining experiments the tincture was prepared from the United States Pharmacopoeial reference powder, as directed in the U.S.P. XI.

*We wish to thank Dr. Henry K. Mohler, of the Department of Therapeutics, for the use of the string galvanometer employed in this research.

The digitalis was injected intravenously in doses of 0.1 c.c. per kilogram, and from one to three minutes were required for each injection. An attempt was made to keep the injection time at two minutes in every instance. The injection was repeated every five minutes until the animal died. In a few instances in which respiration ceased, artificial respiration was employed.

A 1:10,000 aqueous solution of ouabain (Merck) was used. This concentration was estimated on the basis of water-free ouabain. The theoretical lethal dose for the animal was calculated by using the lethal dose (0.092 mg. per kilogram) established by McGuigan and McGuigan.[3] This dose was divided into twelve parts, and one of these parts (0.00766 mg. per kilogram) was injected intravenously every five minutes until the animal died.

In a few additional experiments, two or four injections of digitalis (0.1 c.c. per kilogram) were made before the administration of sodium thiopentobarbital, while the dog was still under ether anesthesia. The ether was then discontinued, and the animal was given as much thiopentobarbital as was needed to maintain surgical anesthesia.

A kymograph was employed to record the fluctuations in blood pressure and gross changes in cardiac activity. A chronometer which marked intervals of six seconds was placed at the zero blood pressure level. In most of our experiments, simultaneous recordings of the blood pressure and electrocardiogram were made.

RESULTS

Digitalis.—There was no conspicuous difference in susceptibility to digitalis between those animals which received sodium pentobarbital intraperitoneally as the anesthetic, and those which first received ether by inhalation for the operative work, and later were given sodium pento-

TABLE I

WEIGHT OF ANIMAL IN KG.	NUMBER OF INJECTIONS	C.C. TINCTURE DIGITALIS INJECTED	MG. PER KG. LETHAL	PER CENT OF THEORETICAL LETHAL DOSE
7.7	12	9.24	120	98
7.0	9	6.3	90	73
13.6	9	12.15	90	73
7.7	8	6.16	80	65
7.7	12	9.24	120	98
9.2	7	6.44	70	57
9.3	11	10.23	110	90
11.8	11	12.98	110	90
10.2	13	13.26	130	106
10.7	10	10.7	100	81
13.9	11	15.29	110	90
7.5	11	8.25	110	90
7.5*	10	7.5	100	81
9.5*	12	11.4	120	98
11.8*	10	11.8	100	81
11.6*	9	10.44	90	73
12.7*	13	16.5	130	106
Average	10.5		105	85

Dogs anesthetized with sodium pentobarbital, in a dose of 35 mg. per kilogram, given intraperitoneally, were used in all of these experiments except those marked by asterisks. In the latter experiments ether anesthesia was used for the operative work, after which the ether was discontinued and sodium pentobarbital was injected intravenously in a 5 per cent solution in doses of 20 mg. per kilogram. Tincture of digitalis (0.1 c.c. per kilogram) was injected intravenously every five minutes. Usually, two minutes were used in making the injection.

The theoretical lethal doses were obtained by multiplying the weights of the animals, in kilograms, by the factor 123 mg. (McGuigan and McGuigan[3]). Considering that 1 c.c. of the official tincture is equivalent to 0.1 Gm. of the standard powder, the lethal dose in mg. per kilogram was ascertained.

barbital intravenously (see Table I). In seventeen such experiments on dogs that weighed between 7.0 and 13.9 kilograms, the quantity of tincture of digitalis, made with the United States Pharmacopoeial reference powder, which was necessary to kill the animal varied from 0.7 (70 mg. of standard powder) to 1.3 c.c. (130 mg. of standard powder) per kilogram of body weight, a range of 85.7 per cent. The average lethal dose was 105 mg. per kilogram. This is approximately 15 per cent less than that reported by McGuigan and McGuigan.[3]

The actual lethal doses for the dogs used in our experiments varied from 57 to 106 per cent of the theoretical lethal dose. The latter was calculated by multiplying the weight of the animal, in kilograms, by 123 mg., which was found by McGuigan and McGuigan[3] to be the average lethal dose for their animals.

That sodium thiopentobarbital (pentothal sodium) definitely decreases the resistance of dogs to digitalis is shown in Table II. No great difference in toxicity was noted between the five animals which weighed from 5.9 to 11.4 kg. and received only sodium thiopentobarbital, and the ten animals which weighed from 6 to 13.2 kg. and first received ether by inhalation, and, later, sodium thiopentobarbital. In one of our animals (see Table II, ‡), 40 mg. per kilogram of sodium

TABLE II

WEIGHT OF ANIMAL IN KG.	NUMBER OF INJECTIONS	C.C. TINCTURE DIGITALIS INJECTED	LETHAL DOSE IN MG. PER KG.	PER CENT OF THEORETICAL LETHAL DOSE
7.7	8	6.16	80	65
7.3	8	5.84	80	65
6.0	8	4.80	80	65
10.0	7	7.00	70	57
12.3	9	11.07	90	73
7.7	10	7.70	100	81
6.8	10	6.80	100	81
13.2	8	10.56	80	65
10.0	7	7.00	70	57
8.6	10	8.60	100	81
11.1*	10	11.1	100	81
11.4*	7	7.98	70	57
5.9*	8	4.72	80	65
8.2*‡	12	9.84	120	98
8.2	9	8.20	90	73
9.1*	11	10.1	110	90
Average	8.9		89	72
6.8†	4	2.72	40	
6.0†	6	3.6	60	
14.0†	7	9.8	70	
9.0†	7	6.3	70	

Sodium thiopentobarbital (sodium pentothal) was used as the anesthetic. In all of these experiments, except those indicated by an asterisk, ether anesthesia was used for the preliminary surgical work, and, after the animal had partially recovered from the ether, sodium thiopentobarbital, in 5 per cent solution, was injected intravenously in doses of 20 mg. per kilogram. In those experiments which are marked with an asterisk, sodium thiopentobarbital, injected intravenously in doses of 20 mg. per kilogram, was the anesthetic. In experiments marked with a †, "Wellcome" tincture of digitalis was used. In all others the tincture of digitalis was made from U.S.P. reference powder, as directed in the U.S.P. XI, and the tincture was injected intravenously in a dose of 0.1 c.c. per kilogram every five minutes, each injection taking approximately two minutes.

thiopentobarbital were required to produce light surgical anesthesia. To maintain this anesthesia, 5 mg. per kilogram of this drug had to be injected intravenously every ten minutes. However, after the second injection of the sodium thiopentobarbital (total, 50 mg. per kilogram), and after the fourth injection of digitalis, artificial respiration had to be maintained for the remainder of the experiment. This was the only animal to which it was necessary to give the full, theoretical, lethal dose of tincture of digitalis, i.e., 120 mg. per kg. of body weight, in order to stop the heart. We found that the lethal dose of the U.S.P reference tincture varied from 70 to 120 mg. per kilogram (standard powder), with an average of 89 mg. per kilogram. This average dose is 16 mg. per kilogram less than that in the experiments in which we used pentobarbital as the anesthetic, 34 mg. per kilogram less than that reported by McGuigan and McGuigan,[3] who used pentobarbital anesthesia, and 52 mg. per kilogram less than that (141 mg.) reported by Haskell et al.,[2] who employed morphine-ether anesthesia. The average number of injections of digitalis was 8.9, and the average dose injected was 72 per cent of the average lethal dose reported by other investigators.[3]

In the four experiments, performed on as many dogs, in which "Wellcome" tincture of digitalis was used, the average number of injections was six, and the average dose was but 50 per cent of the theoretical lethal dose, i.e., 60 mg. of standard powder per kilogram of body weight (see Table II). Although these experiments were few, the results compare favorably with those which we obtained when we used a tincture made from U.S.P. reference powder according to the directions given in the United States Pharmacopoeia XI.

Fig. 1 shows results that are typical of all of the experiments in which either tincture of digitalis made from the official reference powder or the commercial tincture was used. The records in this figure were obtained from a 6-kilogram dog which was anesthetized with ether, by inhalation, for operative purposes. After this was completed the ether was discontinued, and, after the anesthesia became light, 10 mg. per kilogram of sodium thiopentobarbital were injected intravenously between the arrows ↑↓ at *2*. To maintain surgical anesthesia, a second injection of 10 mg. per kilogram was made 16 minutes later, between the arrows ↑↓ at *10*. A commercial tincture of digitalis ("Wellcome"), in the amount of 0.1 c.c. per kilogram of body weight, was slowly injected intravenously at *4, 6, 8, 12, 14,* and *16*. The electrocardiograms below the kymograph record were taken at *3, 5, 7, 9, 11, 13, 15, 17,* and *18,* as indicated in the kymograph record by corresponding numbers. As a result of the injections of thiopentobarbital and digitalis, the blood pressure increased from 123 to 206 mm. of mercury. Following the sixth injection of tincture of digitalis, the heart abruptly began to fibrillate, the blood pressure dropped to the level of atmospheric pressure, and the respirations became accelerated and finally ceased.

As is usually the case when the arterial blood pressure is low (120 mm. of mercury), no irregularity in the heartbeat occurred after the first injection of the sodium thiopentobarbital. Whether the subsequent irregularity (electrocardiogram 11) was caused by the thiopentobarbital or the digitalis we are unable to say, for these two drugs cause similar irregularities. When thiopentobarbital anesthesia was used, we were unable to ascertain what dose of either digitalis or ouabain was

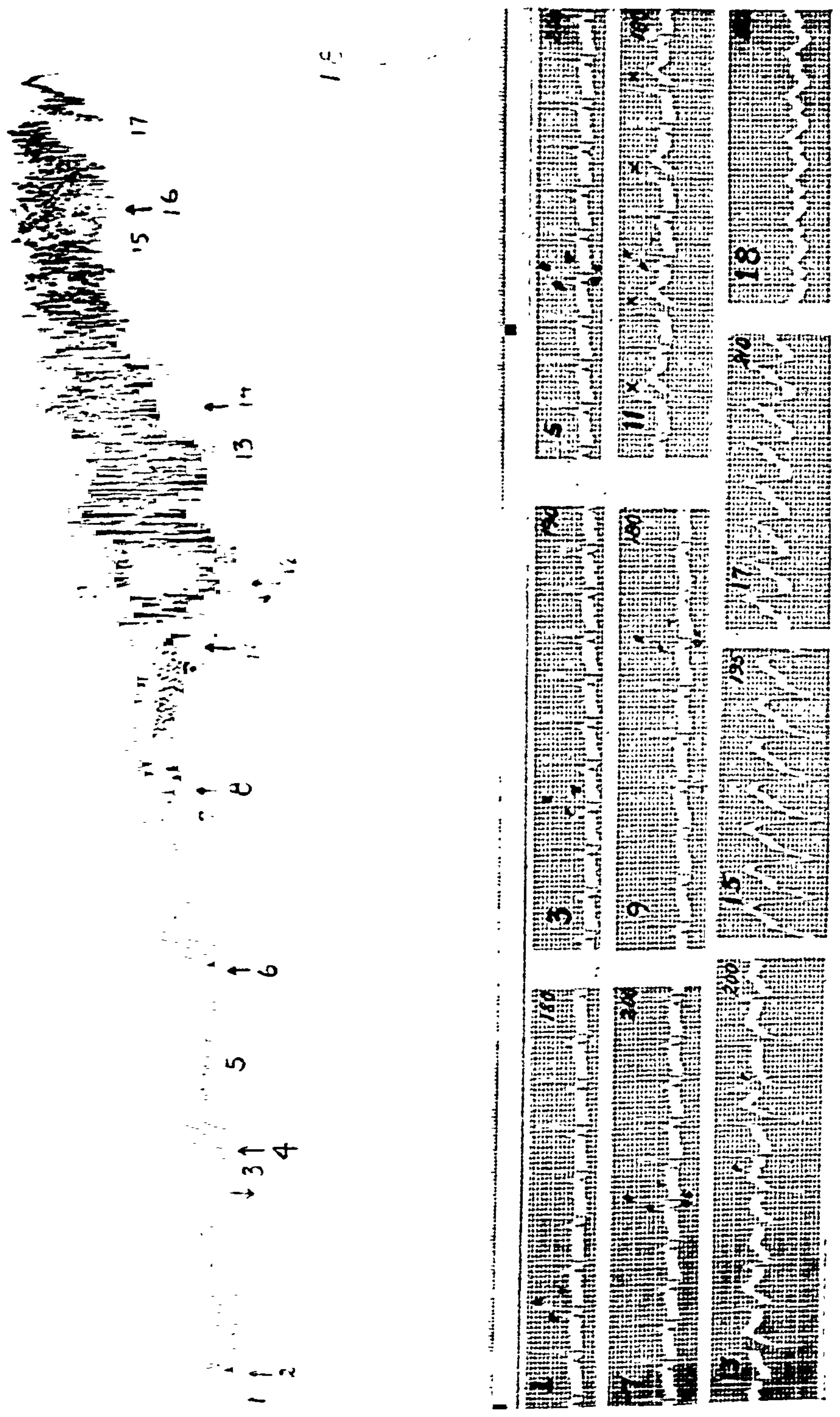

Fig. 1.—Weight of dog, 6 kilograms. Top record is that of the arterial blood pressure, measured with a mercury manometer; below it are the time in intervals of six seconds and zero blood pressure. The numbers to the left in each electrocardiogram correspond to a similar number in the kymographic record itself; the two records were written simultaneously. The numbers to the right of each section of the electrocardiogram indicate the heart rate per minute. For full detail, see text. Record reduced about one-half.

necessary to cause cardiac irregularity because of the fact that the anesthetic itself produced irregularities (premature ventricular contractions) in nineteen of the twenty-seven experiments (see Fig. 2). In one of the experiments in which sodium pentobarbital was used as the anesthetic agent, premature ventricular contractions occurred occasionally. Whether or not they were caused by the anesthetic we do not know. In the remaining sixteen experiments, cardiac irregularity oc-

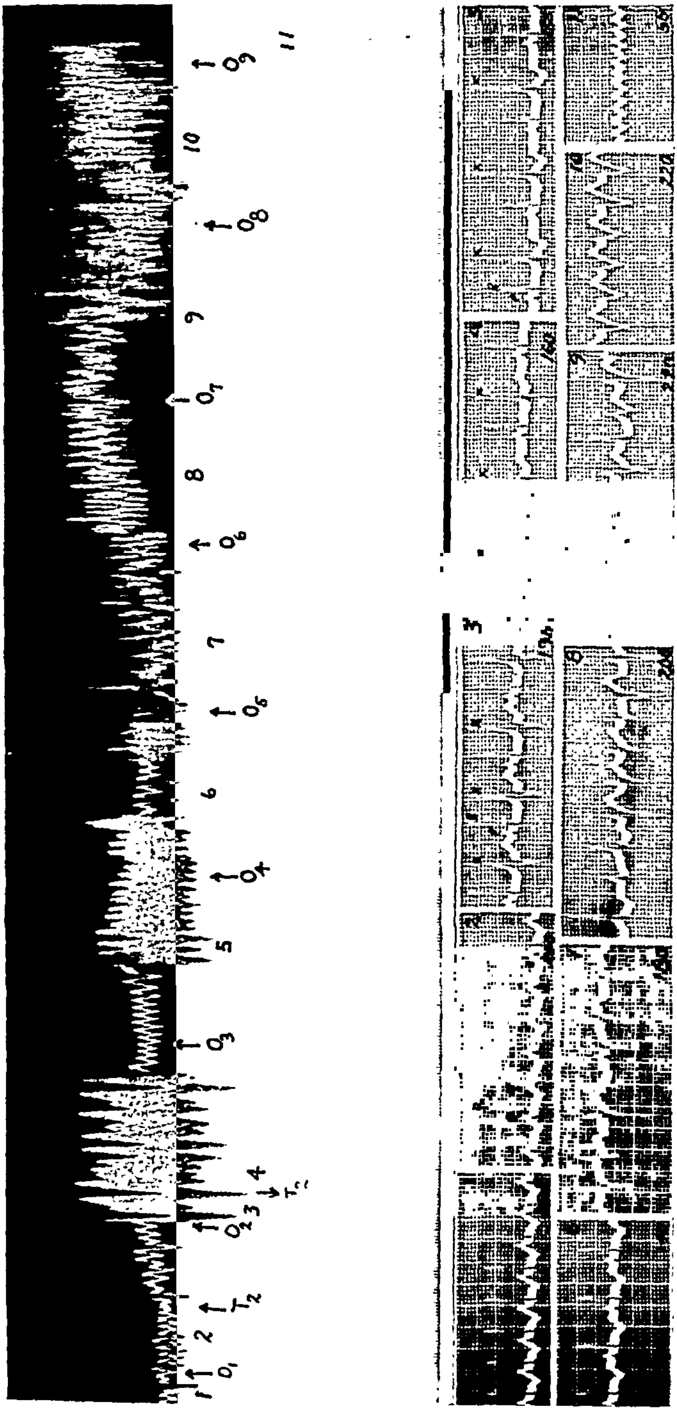

Fig. 2.—Dog, weight 11 kg. Twenty mg. per kilogram of sodium thiopentobarbital were injected intravenously to induce anesthesia. Top record is that of the blood pressure, measured with a mercury manometer, and below this are the time in intervals of six seconds and zero blood pressure. Below the kymograph record there is a series of electrocardiograms. The number in the upper right-hand corner of each segment corresponds to the number in the kymograph record; the two records were taken simultaneously. The numbers in the lower right-hand corners indicate the heart rate per minute. Between the arrows ↑↓ at T_2, sodium thiopentobarbital, in the amount of 10 mg. per kilogram, was injected intravenously. Ouabain, in a dose of 0.85 c.c. of a 1:10,000 solution, was injected intravenously at O_1, O_2, O_3, etc. During the injection of ouabain at O_9, the heart suddenly began to fibrillate, as shown in electrocardiogram 11. Record reduced about one-half.

curred between the fifth and the tenth injections of digitalis. Our average for the entire series of animals was 6.6 injections of 0.1 c.c. per kilogram of tincture of digitalis.

TABLE III

WEIGHT OF ANIMAL IN KG.	NUMBER OF INJECTIONS	LETHAL DOSE IN MG.	LETHAL DOSE IN MG. PER KG.	LETHAL DOSE IN PER CENT OF THEORETICAL LETHAL DOSE
16.8	7	0.90	0.054	59
11.0	8	0.67	0.062	67
11.8	8	0.72	0.061	66
11.8	6	0.54	0.046	50
13.4	9	0.92	0.069	75
7.0	8	0.43	0.060	67
7.7	5	0.30	0.039	42

The toxicity of ouabain in dogs under sodium thiopentobarbital anesthesia (pentothal sodium). The drug was injected intravenously in a 1:10,000 solution, and each dose contained 0.00766 mg. of ouabain per kilogram of body weight. The theoretical lethal dose was calculated by multiplying the weight of the animal, in kilograms, by 0.092 mg. (McGuigan and McGuigan.)

Ouabain.—The results of our experiments with ouabain support our observations on digitalis (see Table III). The number of injections of ouabain (1:10,000 solution) varied from six to nine, and the amount injected ranged from 0.039 to 0.069 mg. per kilogram of body weight. The average lethal dose was found to be 0.056 mg. per kilogram. This is 39 per cent less than the calculated lethal dose. The latter was estimated by multiplying the weight of the animal, in kilograms, by 0.092 mg., which was the average lethal dose in McGuigan and McGuigan's experiments. In our experiments the lethal dose was 25 to 58 per cent less than that reported by other investigators who used pentobarbital as the anesthetic.[3]

Only one record is presented to illustrate the effects of ouabain, for it is fairly representative of all the experiments. The records in Fig. 2 were obtained from an 11 kg. dog which was given sodium thiopentobarbital in a dose of 20 mg. per kilogram, intravenously, for operative purposes. A second intravenous injection of sodium thiopentobarbital, in the amount of 10 mg. per kilogram, was made between the arrows ↑↓ at T_2 as indicated in the kymograph record. We are aware of the possibility that a second injection of sodium thiopentobarbital may be followed by sudden failure of the heart,[7] but in this and other similar experiments this did not occur. After completion of the operation the blood pressure was recorded and electrocardiogram 1 was taken, at 1, as indicated in the kymograph record. At O_1, O_2, O_3, etc., 0.85 c.c. of a 1:10,000 solution of ouabain was injected intravenously, and electrocardiograms were taken approximately two to two and one-half minutes after each injection. These electrocardiograms show that, at first, the heart rate decreased gradually from 204 to 140 beats per minute. Following this decrease, the heart accelerated to 220 beats per minute, and, finally, the ventricle began to fibrillate at a rate of 550 waves per

minute. The blood pressure gradually increased from 144 to 192 mm. of mercury. When the ninth injection of ouabain was about half finished, the heart suddenly began to fibrillate, and the blood pressure dropped to the atmospheric pressure level. Inasmuch as the animal died during this last injection of ouabain, the sum of eight injections was regarded as the lethal dose. The second injection of pentothal sodium was accompanied, as was the first, by premature ventricular contraction (see electrocardiograms 3 and 4).

Blood Pressure.—Not only did pentobarbital and thiopentobarbital modify the effects of digitalis and of ouabain on the heart muscle proper, but, apparently, they also influenced the general arterial blood pressure in a similar manner. When sodium pentobarbital was used as the anesthetic, the control blood pressures in this series averaged 152 mm. of mercury (see Table IV). This was increased by the injections of

TABLE IV

THE EFFECT ON THE ARTERIAL BLOOD PRESSURES IN DOGS UNDER PENTOBARBITAL, ETHER-THIOPENTOBARBITAL, AND THIOPENTOBARBITAL ANESTHESIA OF INJECTING DIGITALIS AND OUABAIN INTRAVENOUSLY

DRUG	ANESTHETIC	EXTREMES IN CONTROL BLOOD PRESSURE	AVERAGE CONTROL BLOOD PRESSURE	EXTREMES IN MAXIMUM BLOOD PRESSURE	AVERAGE MAXIMUM BLOOD PRESSURE	EXTREMES IN BLOOD PRESSURE BEFORE CARDIAC FAILURE	AVERAGE BLOOD PRESSURE BEFORE CARDIAC FAILURE
Digitalis	Pentobarbital	110-178	152	140-211	179	62-186	131
Digitalis	Ether and Thiopentobarbital	114-160	140	160-270	202	80-250	142
Digitalis	Thiopentobarbital	147-190	169	174-240	203	102-185	146
Ouabain	Ether and Thiopentobarbital	120-164	141	140-230	199	90-210	160

digitalis to an average of 179 mm. In these animals, just before the heart began to fibrillate, the average blood pressure was 131 mm. In those experiments in which thiopentobarbital was used after ether had been employed for operative purposes, the control blood pressures, while the animals were under ether anesthesia, averaged 140 mm. of mercury (see Table IV). After withdrawal of the ether anesthesia and following the injection of thiopentobarbital and digitalis, the maximum pressures averaged 202 mm. Just before the heart either ceased beating or began to fibrillate, these general blood pressures averaged 142 mm. In those experiments in which ouabain was used, and those in which sodium thiopentobarbital was the sole anesthetic agent, the average control blood pressures were 141 and 169 mm. of mercury, respectively. These averages were increased to a maximum of 199 mm. Hg, in the former, by ouabain and thiopentobarbital, and, in the latter, to 203 mm. Hg by the thiopentobarbital and digitalis. Just before the heart ceased

beating or began to fibrillate, these average pressures were 160 and 146 mm. of mercury, respectively (see Table IV). It will be noted that the blood pressure reached a higher maximum in all of the experiments in which thiopentobarbital was used as the anesthetic agent.

There were two experiments in which two injections of tincture of digitalis were made while the animals were under ether anesthesia, and two experiments in which four injections were given. In each experiment, after the last injection of digitalis, the ether was discontinued, and sodium thiopentobarbital, in the amount of 20 mg. per kilogram, was injected slowly intravenously. In all four experiments the second injection of thiopentobarbital (10 mg. per kilogram) caused sudden cardiac arrest. In all of these experiments the first injection of pentothal sodium was accompanied by premature ventricular contractions.

DISCUSSION

Judging from our results and those of other investigators, it appears that dogs are not good animals to use for the bio-assay of digitalis. Although we attempted, whenever possible, to maintain identical conditions in all of our experiments (except for weight and age of animals, and these were restricted to a narrow range), nevertheless the lethal dose of digitalis varied more than 85 per cent in dogs under pentobarbital anesthesia. A similar variation in response to digitalis was noted in those of our experiments in which thiopentobarbital was used as the anesthetic agent.

In comparing our results on animals under pentobarbital and thiopentobarbital anesthesia, it is evident that the toxic effect of thiopentobarbital on the heart simply adds to the toxicity of both digitalis and ouabain. We found that the average lethal dose of digitalis, per kilogram, when the animals were under thiopentobarbital anesthesia, was 16 mg. less than that for animals under pentobarbital anesthesia. If these results are compared with those of McGuigan and McGuigan,[3] the difference becomes 34 mg. per kilogram less. Similarly, when the average lethal dose of ouabain for the dogs under thiopentobarbital anesthesia is compared with that reported by the above investigators, it is found that our animals required 39 per cent less ouabain per kilogram.

Our studies on blood pressure support the view that it may make some difference, with respect to the action of digitalis and ouabain, whether one uses pentobarbital or thiopentobarbital anesthesia. The average maximum blood pressures after the injection of either tincture of digitalis or ouabain were 20 mm. of mercury higher in the animals under thiopentobarbital anesthesia.

The difference between the toxic effect of digitalis and ouabain on dogs under thiopentobarbital (pentothal) anesthesia and dogs under pentobarbital anesthesia is to be attributed, we believe, to the toxic action of pentothal on cardiac muscle. Of the seventy-nine dogs which

received sodium thiopentobarbital, a cardiac irregularity (premature ventricular contractions) occurred either during, or immediately after, the completion of the injection in fifty-five, an incidence of over 69 per cent. If we include, also, those injections which were made to maintain anesthesia, we find that premature ventricular contractions were noted after 105 of the 143 injections (73 per cent).

SUMMARY

1. Dogs are not satisfactory animals for the bio-assay of digitalis.
2. Anesthetic agents play a rôle in determining the toxicity of digitalis and ouabain. When sodium thiopentobarbital is used the amounts of either digitalis or ouabain which are needed to bring about cessation of cardiac activity are much less than those required when sodium pentobarbital is the anesthetic agent.

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THE INCIDENCE OF SYPHILITIC AORTITIS IN A REPRESENTATIVE MUNICIPAL HOSPITAL

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THE incidence of syphilis has been shown to be greatest in the lower economic strata of society.[1, 2, 3, 4, 5] Turner,[6] in a study of 10,000 consecutive cases of syphilis, found that a diagnosis of cardiovascular syphilis had been made in 10.1 per cent of the cases of late syphilis. Bruusgaard[7] followed 473 patients who had received no treatment for their early syphilis, and found that 12.8 per cent developed cardiovascular syphilis. It is logical to assume, therefore, that syphilis of the cardiovascular system would constitute a major medical problem in hospitals (city, county, or state) which furnish medical care to those in the lowest economic groups. Since, in all cases, syphilitic valvulitis and aneurysm evolve from a pre-existing syphilitic aortitis, the present study has been undertaken in an attempt to ascertain the incidence of syphilitic aortitis in the wards of the Cincinnati General Hospital.

This hospital has 925 beds, and serves the low-income groups of the population of Cincinnati. For over ten years, less than 10 per cent of the patients who were admitted were able to pay even a small portion of the cost of hospitalization. Negroes constitute approximately 35 per cent of the total number of patients who are admitted each year.

Only cases in which a histologic diagnosis of syphilitic aortitis had been made by members of the Department of Pathology were included in this study. All such cases which were encountered between 1926 and 1937, inclusive, were reviewed. Cases in which the aortitis was accompanied by aneurysm, valvulitis, or gumma were omitted from consideration.* Table I shows the incidence of these cases.

Statistical conclusions drawn from autopsy material must be qualified before they can be applied to a living population. The following paragraphs discuss the variants encountered in this study:

Cases which were encountered in a sample period (1936 to 1937) were studied in detail in order to ascertain the age incidence at death and autopsy, as well as the number of patients with syphilitic aortitis who had had antisyphilitic therapy. Of the 138 patients who were studied, twenty-seven had had some antisyphilitic treatment, but only seven had had what may be considered sufficient therapy. The remaining patients were either too ill on admission for specific questioning, gave a history of untreated syphilis, or denied any knowledge of infection. As is shown in Table II, the mortality among the young and those over 40 was higher

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TABLE I

HOSPITAL STATISTICS RELATIVE TO SYPHILITIC AORTITIS FOR THE YEARS 1926 TO 1937, INCLUSIVE

YEAR	HOSPITAL ADMISSIONS	DEATHS	AUTOPSIES	NO. CASES OF SYPHILITIC AORTITIS*	APPROXIMATE NUMBER OF CASES OF SYPHILITIC AORTITIS PER ANNUM
1926	11,518	1,273	422	31 (7.3%)	841
1927	12,177	1,253	483	37 (7.6%)	925
1928	13,086	1,374	553	39 (7.1%)	929
1929	13,832	1,530	664	79 (10.4%)	1,435
1930	14,580	1,491	644	68 (10.5%)	1,531
1931	15,172	1,554	572	76 (13.2%)	2,003
1932	16,116	1,555	676	53 (7.8%)	1,257
1933	16,777	1,587	675	53 (7.8%)	1,309
1934	16,903	1,785	734	54 (7.3%)	1,234
1935	16,234	1,679	618	72 (11.5%)	1,867
1936	16,629	1,702	813	74 (9.1%)	1,533
1937	15,834	1,611	830	64 (7.7%)	1,219

*Diagnosis made at autopsy; uncomplicated by aneurysm, valvulitis, or gumma.

TABLE II

PERCENTAGE OF DEATHS (FROM ALL CAUSES) AND AUTOPSIES OCCURRING IN VARIOUS AGE GROUPS DURING THE SAMPLE YEARS 1936 AND 1937

AGE GROUP	PER CENT OF TOTAL DEATHS (3313) DURING 1936 AND 1937	PER CENT OF TOTAL AUTOPSIES (1643) DURING 1936 AND 1937
0–19	24.7%	23.0%
20–39	18.6%	14.4%
40–59	28.0%	30.3%
60–up	28.7%	32.3%

than between the ages of 20 and 39, although the per cent of autopsies for each age group was roughly proportional to the per cent of deaths in that group. Because syphilitic aortitis almost never occurs in children,[8, 9] they merely act as a statistical diluent. Also, a preponderance of the aged does not detract from the value of this study, for the majority of syphilitic infections are acquired during the second and third decades of life[10, 11]; therefore, microscopic evidence of syphilis in patients over 40 is an indication of an infection which was probably acquired earlier in life. This fact tends to compensate for the lower death rate among adults under 40.

There is a widespread assumption that it is comparatively easy to obtain permission for a post-mortem examination from relatives of colored patients. However, a comparison of the number of negroes admitted to the hospital (approximately 35.0 per cent) with the percentage of negroes autopsied (39.6 per cent), for the years 1936 and 1937, shows only a 4.6 per cent difference in this respect.

It is acknowledged that routine section and microscopic examination of the aorta will unavoidably miss an unestimated number of actual

lesions. Not only is syphilitic involvement of the cardiovascular system focal in character, but sections are not always taken routinely from all grossly abnormal areas.

An autopsy group is, in itself, not an entirely fair sample of the population. The patients were not only hospitalized for one reason or another, but they did not survive.

Among the variants which have been discussed, there are two which make for an underestimation of the incidence of syphilitic aortitis, namely, (1) the fact that the patients in one group were less than 20 years old, and (2) that there must have been a number of patients with unrecognized syphilitic aortitis.

On the other hand, syphilitic aortitis is supposed to have a detrimental effect on the ability of a patient to combat another disease. The modifying action of syphilitic aortitis upon the death rate from infections and diseases of senescence has not yet been ascertained. Vonderlehr[12] has calculated that syphilis reduces the life expectancy 17.0 per cent (4.8 years) for a white man of 30, and 30.5 per cent (7.1 years) for a negro 30 years of age. McDaniel,[5] in a study of people on the relief rolls of Fulton County, Georgia, found that syphilis constitutes a definite economic handicap; 17 per cent of those between the ages of 20 and 40 were partially incapacitated, and 16 per cent of those over 50 were totally incapacitated. These factors tend to neutralize the variants discussed in the previous paragraph. The exact degree of neutralization cannot be ascertained; nevertheless, it is considered that the application of the data derived from the autopsy material to the general population will give reasonably accurate information—at least to the important extent of determining whether the yearly incidence of syphilitic aortitis is approximately 1000, or 100.

Of the 7,683 autopsies which were performed between 1926 and 1937, inclusive, microscopic evidence of syphilitic aortitis (excluding all developmental complications) was found in 700, or 9.1 per cent.

Lamb,[13] in a survey of the post-mortem material at the Presbyterian Hospital, New York, found that the incidence of syphilitic aortitis, per se, was 5.1 per cent. Welty,[14] at the Philadelphia General Hospital, found that the incidence of syphilitic aortitis, excluding aneurysm and valvulitis, was only 4.2 per cent in a large post-mortem group in which negroes formed 40 per cent of the total. Carr[15] collected eighty-three cases of syphilitic aortitis, per se, from a series of 955 autopsies[16] which were performed in 1929 at the Cook County Hospital, an incidence of 8.7 per cent. Such variations in the incidence of syphilitic aortitis in autopsy groups depend, in great measure, on differences in the social status of the source population, and on the number of negroes who are included.

It is to be expected that approximately 8 per cent of the white, and 25 per cent of the negro, patients in a hospital that cares for the indigent

sick will have syphilis.[2, 5, 17, 18] If the above percentages are applied to the autopsy group herein studied, the calculation shows that there should be 1,132 patients with syphilis (14.6 per cent). Since not all patients with syphilis have syphilitic aortitis, and estimations of its incidence vary from 50 to 90 per cent,[19, 20, 21] if we apply an average figure of 70 per cent to our post-mortem material we should have 792 cases of syphilitic aortitis, or 10.3 per cent. This predicted percentage is comparable to the actual incidence, which was 9.1 per cent.

Judging from the calculated incidence of syphilitic aortitis, column 6, of Table I, indicates approximately the number of patients with syphilitic aortitis who were admitted to the Cincinnati General Hospital during each year of the period between 1926 and 1937, inclusive.

DISCUSSION

It has been calculated that at least 1,200 patients with syphilitic aortitis are admitted to the Cincinnati General Hospital each year, which means that the hospital has a larger number of cases of this disease than of any other. This brings up the problem of diagnosis and treatment. Since the latter has been amply reviewed, it will not be considered here. However, the diagnosis of syphilitic aortitis, uncomplicated by its late developmental complications, would seem to merit more practical consideration than it has yet received.

The clinical diagnosis of "uncomplicated syphilitic aortitis" has been discussed by Moore,[22] but the validity of such a diagnosis has not been absolutely established.[23, 24] It would seem that, for practical purposes, and because of the large number of cases involved, the problem might be solved by a better application of our knowledge of the pathology of syphilis. Except during the relatively short, early, mucocutaneous infectious, and late visceral, stages, syphilis in its latent period is not moribund, but smoldering, and is slowly but surely destroying irreplaceable vital tissue.[12, 19] We are unable to predict who will develop, and who will escape, the disastrous developmental complications of syphilitic aortitis. Therefore, it is suggested that "probable syphilitic aortitis" be added to each diagnosis of late, latent syphilis.

SUMMARY

1. A study of the autopsies performed at the Cincinnati General Hospital from 1926 to 1937, inclusive, revealed that the average incidence of syphilitic aortitis (excluding all developmental complications) was 9.1 per cent.

2. At least 1,200 patients with syphilitic aortitis are admitted to the Cincinnati General Hospital each year.

3. It is suggested that each patient with late, latent syphilis, who has not had adequate specific treatment, should be considered as having active syphilitic aortitis.

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THE CARDIOVASCULAR SYSTEM IN PULMONARY TUBERCULOSIS

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THERE have been some misconceptions concerning the relation of certain types of heart disease to active pulmonary tuberculosis. Mitral stenosis has been considered rare in cases of pulmonary tuberculosis, as also have other forms of chronic valvular heart disease which are frequently associated with chronic passive congestion. These statements were formerly widely accepted, but, in view of our present knowledge, they are not justified.

CONGESTIVE FAILURE

The difficult problem of differentiating between the congestive failure of heart disease and the manifestations of pulmonary tuberculosis is frequently encountered. The symptoms are often identical, namely, cyanosis, shortness of breath on effort, orthopnea, cough, diminished vital capacity, palpitation, and edema. In cases of primary heart disease, evidence of a rheumatic or syphilitic cardiovascular process is usually obtained from the history, physical examination, and roentgenologic studies. The presence of any of the different types of cardiovascular disease, namely, rheumatic, syphilitic, hypertensive, or arteriosclerotic, may of itself account for the signs above mentioned. However, they may occur in certain instances in association with pulmonary tuberculosis alone, either active or healed.

Clinically, it is possible to differentiate between right- and left-sided heart failure, which is a point of considerable importance, especially when mechanical interference in pulmonary tuberculosis is being considered. The right side of the heart possesses a large physiologic factor of safety which enables it to cope adequately with extensive disease of the pulmonary vascular bed. Left-sided failure is a serious condition, and carries a greater risk. It results from hypertension, aortic valvular disease, or infarction of the left ventricle. These are not common factors in pulmonary tuberculosis.

CAUSE OF SYMPTOMS

The alteration of the alveolar walls which interferes with adequate aeration of the blood in its passage through the lungs gives rise to anoxemia. Reduction in the area of the pulmonary vascular bed, increasing pulmonary peripheral resistance and leading to hypertension of the pulmonary circuit, plays an important role in the genesis of failure of the right side of the heart in chronic pulmonary disease. The other causes of right ventricular strain are mitral stenosis, pulmonic stenosis and insufficiency, pulmonary endarteritis, organic tricuspid in-

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sufficiency, marked pulmonary fibrosis, and pulmonary emphysema. In pulmonary tuberculosis, the latter two are important causes of cardiac insufficiency.

CARDIAC INVOLVEMENT IN PULMONARY TUBERCULOSIS

Involvement of the heart in pulmonary tuberculosis may be divided into (1) effects of adhesions upon a normal heart; (2) results of tuberculous pericarditis, and (3) results of tuberculous myocarditis. Before describing other types, it is appropriate to consider cases in which the heart is normal, as it usually is in tuberculosis.

THE HEART IN TUBERCULOSIS

In cases of pulmonary tuberculosis, the heart is described as being characteristically small because of the fact that it is of the dropped or pendulum type. Some have regarded this as a congenital condition, as a result of which poor circulation in the lungs and elsewhere in the body paves the way for the development of pulmonary tuberculosis, but the fact is that the more vascular tissues are the ones which are susceptible to tuberculosis, not the avascular tissues. Others are of the opinion that it is an acquired abnormality, that the small heart is the result of a tuberculous toxemia, producing wasting, loss of tone, and deterioration of heart muscular tissue, as well as of muscle and other tissue throughout the body. However, the heart in pulmonary tuberculosis bears a normal relation to the body weight.

TUBERCULOUS PERICARDITIS

Tuberculosis of the heart is by no means rare, although, when one considers the large number of cases of tuberculosis, involvement of the heart is at least infrequent.[1] Tuberculous pericarditis is by far the most frequent and most important form. It occurs in about 1 per cent of all autopsies, and in about 3 per cent of autopsies on tuberculous patients. It has been observed in all decades of life, from the second to the seventh. At the Philadelphia General Hospital it is twice as frequent in the colored race as in the white.

There are three main types of tuberculous pericarditis which are important from the clinical as well as from the pathologic standpoint: (1) So-called primary pericarditis, in which the tuberculous involvement is limited, as far as one can ascertain clinically, to the pericardium. The lungs are free from involvement, as are other parts of the body except the mediastinal nodes. In these cases, the disease not infrequently terminates in generalized miliary tuberculosis. (2) Pericarditis associated with either active or healed tuberculosis of the lung. (3) Pericarditis associated with tuberculosis elsewhere in the body, particularly bone tuberculosis.

SYMPTOMS OF TUBERCULOUS PERICARDITIS

The symptomatology of this condition varies with the type and degree of involvement. Its presence during the course of active pulmonary *tuberculosis may be masked by the symptoms and signs of the pulmonary disease.* In a typical case of so-called primary tuberculous pericarditis, the onset is usually insidious, with signs of an upper respiratory infection. Patients complain of lassitude and general weakness, and may have a slight fever for weeks. Precordial pain is not infrequently observed; a friction rub may be audible for long periods of time, and yet the patient may complain of comparatively little discomfort. A patient with tuberculous pericarditis may feel well enough to walk about, but one with rheumatic pericarditis is ill, and confined to bed. The latter is also true of the patient with the pericarditis which occurs in the terminal stages of nephritis. With the development of moderate to marked effusion, evidence of cardiac embarrassment appears. Obvious dyspnea is present only when the effusion is very large. Congestive heart failure is practically never observed except as a terminal event. The bases of the lungs remain surprisingly clear, even when the effusion is very large. In one-third of the cases there is a leucopenia, with a relative neutrophilia, but no typical hematologic changes occur in tuberculous pericarditis.

THE DIAGNOSIS OF TUBERCULOUS PERICARDITIS

The diagnosis of tuberculous pericarditis must be established both anatomically and etiologically. The clinical features of tuberculous pericarditis differ in no way from those of other forms of pericarditis. There may be an effusion, or a thickened pericardium. The fact that it is tuberculous is relatively easy to establish when the patient has tuberculosis of the lung. In fact, pericarditis which occurs when there is active tuberculosis anywhere in the body is nearly always tuberculous. The chief difficulty in differential diagnosis arises in cases of the so-called chronic, primary type. This must be differentiated from rheumatic pericarditis and that associated with the terminal stage of nephritis. The following points are of help. Rheumatic pericarditis attacks children and young adults who usually present other manifestations of rheumatic fever or carditis. It is rare in later life. Tuberculous pericarditis occurs frequently in the later decades. The incidence of rheumatic pericarditis is no greater in one race than another, whereas two-thirds of the cases of tuberculous pericarditis occur in the colored race. Pain is a very prominent symptom of rheumatic pericarditis, and the patient is quite ill and uncomfortable. Pain may be entirely absent in tuberculous pericarditis. In fact, the patient may appear quite comfortable and be able to walk about, despite the fact that he has a small effusion and a rather loud friction rub over the precordium. There are no joint involvement, no murmurs of cardiac origin, and no associated pulmonary congestion. The effusion is hemorrhagic, and some-

times tubercle bacilli may be recovered from the aspirated material. After aspirating the fluid and injecting air, the heart is found not to be enlarged. Thickening of the pericardium, with calcification, may be present. Generally, the prognosis is poor, although cases are occasionally observed in which the patient recovers from the acute stage, and develops a chronic, adherent process.

TABLE I

DIFFERENTIAL DIAGNOSIS OF TUBERCULOUS AND RHEUMATIC PERICARDITIS

	TUBERCULOUS PERICARDITIS	RHEUMATIC PERICARDITIS
Age	Usually occurs in the later decades	Occurs in children or young adults who present other manifestations of rheumatic fever or carditis. Rare in later life
Racial predilection	Two-thirds of cases occur in the colored race	None
Pain	Often absent	Prominent symptom
Activity	Patient may appear comfortable, and walk about	Patient quite ill and confined to bed.

TREATMENT OF TUBERCULOUS PERICARDITIS

The treatment of tuberculous pericarditis with effusion consists in withdrawal of the fluid, especially if the effusion is large, and replacing it with air. When it progresses to the adherent or constrictive stage, some other form of operative procedure may be indicated, as advocated by Beck and Griswold.[2]

OTHER FORMS OF PERICARDITIS

The rheumatic type of pericarditis occurs in association with rheumatic valvular heart disease, most frequently aortic or mitral, or even both. Congestive pulmonary phenomena are usually present. The effusion is serofibrinous and sterile. The heart is enlarged, active rheumatic fever is usually present, and the patient is obviously acutely ill.

The pericarditis which is associated with advanced nephritis rarely offers any difficulty in diagnosis.

TUBERCULOSIS OF THE MYOCARDIUM

Tuberculosis of the myocardium is apparently quite rare; only about 222 cases have been reported to date. Its actual incidence is probably greater than this, however, for microscopic involvement may easily be missed on routine necropsy examination. Three types have been observed: (1) The infiltrating type, which most frequently involves the auricles, is caused by spread of the tuberculous process from the pericardium to the myocardium. Clinically, the inception of auricular involvement may be manifested by the appearance of auricular extrasystoles, and, rarely, by auricular fibrillation.[3] Involvement of the ventricular muscle is much less common, but, nevertheless, extensive de-

struction has been observed. Caseous infiltration has been known to destroy one-half, or more, of the thickness of the ventricular wall, and may extend even to the endocardium.[4] (2) Nodular involvement of the myocardium may also occur as a part of a generalized miliary tuberculosis, but this is very infrequent. (3) Finally, there is an interstitial tuberculous myocarditis which resembles, to some extent, that caused by any fever, but is distinguished by the fact that the central infiltration, which comprises small lymphocytes, endothelial cells, a few leucocytes, and, occasionally, a Langhans cell, is much more diffuse. This type has been described by Gallavardin.[5]

TUBERCULOSIS OF THE ENDOCARDIUM

Tuberculous endocarditis is quite rare, but a few authentic cases have thus far been reported. At Duke University, Baker[6] found endocardial tuberculosis in six of 900 consecutive necropsies on patients with pulmonary tuberculosis. In five instances, small tubercles were scattered over all parts of the endocardium as part of a generalized miliary infection. In one instance the endocardial involvement resulted from extension of a pericardial and myocardial process through the cardiac wall. White[7] reports only one case of diffuse involvement along the line of closure of a valve in which the diagnosis was probably correct. Dr. Joseph Walsh[8] states that he saw two cases of tuberculosis of the mitral valve in which the organisms were demonstrated in the tissues microscopically. The toxic action of a tuberculous process somewhere in the body does not result in sclerosis of the endocardium, or myocardial fibrosis, or calcified valvular lesions.

EXTRACARDIAC TUBERCULOSIS

Tuberculous mediastinitis may encroach upon the branches of the pulmonary artery, causing a systolic murmur and thrill at the pulmonic area, and accentuation of the pulmonic second sound. This involvement may lead ultimately to right ventricular strain and failure.

Tuberculosis is occasionally the underlying cause of Pick's disease, or polyserositis. Although cardiac failure is rare in ordinary cases of tuberculosis, we have occasionally seen patients with tuberculous pericarditis develop enough ascites to require tapping. Pseudocirrhosis of the liver, which was associated with the pericarditis, was the underlying cause. In these cases the liver function may be good, and there is no pretibial edema.

THE EFFECTS OF PULMONARY TUBERCULOSIS ON THE HEART

Indirectly, pulmonary tuberculosis may produce significant effects on the heart. Spontaneous pneumothorax places a sudden strain on the heart which leads to profound shock. The pulse becomes rapid, weak, and thready, and, not infrequently, death is the result. Even induced pneumothorax, which shifts the heart and mediastinal structures to one side, whether or not inflammatory lesions have partially fixed these

structures, produces a strain on the myocardium. Dyspnea, cyanosis, and tachycardia are added to the already existing symptoms until the heart becomes adjusted to the altered dynamics. The occurrence of these symptoms indicates that treatment should be conservative during the early stages of artificial pneumothorax.

Extensive chronic pulmonary involvement, which is so frequently associated with widespread pulmonary fibrosis, affects the heart unfavorably. It is quite difficult to evaluate the dyspnea, cyanosis, tachycardia, and fatigability in such cases, because most of these symptoms are common to both pulmonary tuberculosis and myocardial disease. Such extensive changes in the lungs are found to have a bad effect on the myocardium, resulting particularly in increased strain on the right side of the heart.

Paroxysmal tachycardia and paroxysmal auricular fibrillation have been known to occur in cases of tuberculosis. The cause of these disturbances in the mechanism of the heartbeat may be functional, and also obscure, just as it often is in patients who do not have pulmonary tuberculosis. If there is extensive involvement of the mediastinal lymph nodes, there is the possibility that, in some cases, encroachment on the sympathetic and vagus nerves may be an important factor in the production of these abnormalities of the cardiac mechanism. A-V nodal tachycardia is the type most frequently associated with tuberculosis.

OTHER TYPES OF HEART DISEASE IN PULMONARY TUBERCULOSIS

The patient who has pulmonary tuberculosis, or some other form of the disease, may have had, or may develop, other kinds of heart disease. Rheumatic heart disease, particularly mitral stenosis, is observed not infrequently in association with tuberculosis. The incidence is said to be similar to that in other conditions in comparable age groups. The same is true of syphilitic aortitis and aortic insufficiency.

In cases of congenital heart disease, tuberculosis, usually of the miliary type, has often been regarded as the cause of death. The impression gained from hospital records, however, is distinctly against this. Death usually results from the congenital defect itself, or from superimposed bacterial endocarditis, and not infrequently from pneumonia.

Hypertensive heart disease is not seen frequently in association with tuberculosis. Ayman[9] found one instance among 240 cases. Fifteen per cent of all adults, and 23 per cent of those who die after the age of 50 years have hypertension.[10] A careful study of blood pressure in cases of tuberculosis, made at the White Haven Sanatorium, repeated at definite intervals, and carried on over a period of ten years, revealed that the prevalent idea that the blood pressure is generally low in cases of tuberculosis is erroneous. The blood pressure was usually at the lower limits of normal. In the advanced age groups, a high reading was often found. Only those patients who were quite ill, and had extensive

disease, had an abnormally low blood pressure, and, as they improved, there was a tendency for the blood pressure to rise. The upper and lower limits of systolic pressure which were accepted as normal were 150 and 110 to 100, respectively. Any diastolic pressure over 90 was considered abnormally high. These limits, as judged by our present-day standards, are high, and lower levels will be accepted in the near future.[11]

Coronary occlusion is seldom observed in cases of tuberculosis. Although tuberculous arteritis occurs, it has been observed but rarely in the coronary arteries,[12] and is usually confined to the smaller branches. In one reported case it did involve a comparatively large coronary branch. Three types of involvement have been observed: (1) tubercles in the intima; (2) tuberculous invasion of the adventitia, with focal or diffuse involvement of the entire wall; and (3) noncellular thickening of the intima, which, if sufficiently extensive, may lead to vascular occlusion—the so-called "contact endarteritis."

Pulmonary embolism and thrombosis often simulate coronary occlusion.[13] The manifestations include a sudden onset of precordial oppression, or actual pain, marked dyspnea or tachycardia, cyanosis or ashen pallor limited to the upper part of the body, apprehension, a rapid, feeble pulse, collapse of the peripheral circulation, a low blood pressure, and profuse perspiration. Recently, pulmonary thrombosis has been found more frequently at the White Haven Sanatorium, and, occasionally, the diagnosis is made ante mortem.

STUDY OF PATIENTS ADMITTED TO THE WHITE HAVEN SANATORIUM

A study was made of the patients who were admitted to the White Haven Sanatorium during 1935. Those with heart disease were grouped according to age and the status of their tuberculosis. There were, in all, 418 patients, 238 men (57 per cent), and 180 women (43 per cent). Of the men, twenty-one (8.8 per cent), and, of the women, eight (4.4 per cent), were thought to have heart disease. Seventy of the patients who were admitted during 1935 died; forty-eight of these were men (68 per cent), and twenty-two were women (31.4 per cent). Thirty post-mortem examinations were performed, twenty-three on men (76 per cent), three of whom had had a diagnosis of heart disease ante mortem, and seven on women (23.3 per cent). At post-mortem examination it was discovered that ten additional patients had heart disease; seven of these were men, and three were women. Of the thirteen autopsied patients who had heart disease, seven had far-advanced pulmonary tuberculosis, four had anthracosilicosis and two were nontuberculous. Of the ten male patients, three had arteriosclerotic cardiovascular disease, three had arteriosclerosis with cardiac hypertrophy, three had cardiac hypertrophy, and one had an aortic vegetation, the etiology of which was not stated. Of the three women, two had myocardial degeneration with hypertrophy, and one had cardiac hyper-

trophy. Among the remaining seventeen post-mortem examinations, only three normal hearts were found. In the cases in which heart disease was not diagnosed during life, fourteen post-mortem examinations revealed that the pericardium was adherent, in eleven cases on both sides, in two on the right side, and in one on the left side. The myocardium was pale, flabby, and thin in eleven instances, particularly that of the right ventricle.

TABLE II

PATIENTS ADMITTED TO THE WHITE HAVEN SANATORIUM IN 1935

AGE	WITH HEART DISEASE MALE	WITH HEART DISEASE FEMALE	WITHOUT HEART DISEASE MALE	WITHOUT HEART DISEASE FEMALE	TOTAL
7–19 years	1	0	19	26	46
20–29 years	4	4	58	86	152
30–39 years	3	2	46	42	93
40–49 years	3	2	55	12	72
50–59 years	5	0	32	3	40
60 and over	5	0	7	3	15
Total	21	8	217	172	418

CLASSIFICATION

STAGE OF DISEASE	WITH HEART DISEASE MALE	WITH HEART DISEASE FEMALE	WITHOUT HEART DISEASE MALE	WITHOUT HEART DISEASE FEMALE	TOTAL
Minimal	1	2	20	17	40
Moderately advanced	2	0	28	39	69
Far advanced	12	3	67	48	130
Nontuberculous	6	3	34	13	56
Miliary tuberculosis	0	0	0	1	1
Still in Sanatorium	0	0	68	54	122
Total	21	8	217	172	418

The records of all patients with pulmonary tuberculosis who were admitted to the Philadelphia General Hospital during 1935 were analyzed. There were, in all, 1585 patients, 1017 men (64 per cent), and 568 women (36 per cent). In this series, 1000 completed records were available for study. In addition to their pulmonary tuberculosis, a clinical diagnosis of some form of cardiovascular disease was made in 8.7 per cent. These cases are summarized in Table III. It is to be noted that practically every variety of cardiovascular disease was found in association with pulmonary tuberculosis.

SUMMARY

In pulmonary tuberculosis, the heart is normal in most instances. However, various etiologic types of heart disease may be associated with pulmonary tuberculosis. In three to five cases out of a hundred, tuberculosis may involve either the pericardium, the myocardium, or, rarely, the endocardium. The signs, symptoms, and methods of diagnosis are discussed, and their significance emphasized. Tuberculosis specialists too often overlook the presence of cardiac abnormalities because of the fact that the symptoms are similar to those caused by pulmonary disease.

TABLE III

CLASSIFICATION OF PATIENTS WITH PULMONARY TUBERCULOSIS AND CARDIOVASCULAR DISEASE ADMITTED TO THE PHILADELPHIA GENERAL HOSPITAL IN 1935

MALES	FEMALES
Arteriosclerotic cardiovascular disease:	
19 without complications	7 without complications
1 with auricular fibrillation and silicosis	2 with hypertension
2 with hypertension	1 with rheumatic valvular disease
1 with coronary occlusion	1 with coronary occlusion
1 with hypertension and chronic proliferative pericarditis	
24	11
Total: 35 (24 males, 11 females)	
Valvular disease:	
2 mitral insufficiency (rheumatic etiology?)	3 rheumatic mitral insufficiency
1 rheumatic—double mitral and aortic	
3	3
Total: 6 (3 males, 3 females)	
Hypertensive cardiovascular disease:	
5 without complications	2 without complications
1 with a positive Wassermann	1 with arteriosclerosis
	1 with mitral insufficiency and a positive Wassermann
	1 with mitral insufficiency
6	5
Total: 11 (6 males, 5 females)	
Luetic cardiovascular disease:	
5 without complications	
1 with rheumatic endocarditis	
1 with aneurism	
1 with coronary occlusion	
8	
Total: 8 males	
Pericarditis:	
1 (chronic fibrous) without complications	1 without complications
1 with hypertension and cardiac hypertrophy	1 with rheumatic heart disease
2	2
Total: 4 (2 males, 2 females)	
Endocarditis:	
Total: 1 female	1 of aortic valve
Myocardial degeneration:	
5 unconfirmed	4 unconfirmed
1 confirmed by laboratory examination	3 confirmed by autopsy
1 confirmed by autopsy	1 autopsy negative
1 toxic myocarditis	1 toxic myocarditis
1 congestive heart failure (etiology?)	1 toxic myocarditis, autopsy negative
1 hypertrophy (etiology?)	1 myocardial hypertrophy revealed by autopsy
1 right ventricular hypertrophy revealed by autopsy	
11	11
Total: 22 (11 males, 11 females)	

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NOTE ON ELECTROCARDIOGRAPHIC NOMENCLATURE

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NAMES are short cuts of identification and should be as simple as possible. Long, descriptive phrases ought to be avoided. One such phrase, which is now accepted by virtue of its inclusion in the *Nomenclature and Criteria for Diagnosis of Diseases of the Heart*,[1] is "Elevation (or Depression) of S-T (or R-T) Segment at Origin." Others describe it as the S-T junction, or take-off.

R-T OR S-T JUNCTION

For some time, in my own descriptions of electrocardiograms, I have used the letter J to represent junction, and have used a numeral as subscript to indicate the lead, thus: J_3 or J_4. If this idea were followed, the headings "50. Unusual Elevation of S-T (or R-T) Segment at Origin," and "51. Unusual Depression of S-T (or R-T) Segment at Origin" could be written simply "50. High (or Elevated) J," and "51. Low (or Depressed) J."

The partial description of Lead I in a case of infarction of the anterior wall of the left ventricle of a few days' duration might be J_1 plus, or J_1+, T_1 minus, or T_1-. In brief, it would be written J_1+, T_1-.

To indicate the abnormalities with greater precision, the suggestion of McGinn and White[2] may be followed, giving in tenths of a millivolt the deviation from the isoelectric level. If the take-off is elevated 0.1 mv., and T is depressed 0.3 mv., the written description would be $J_1 + 1$, $T_1 - 3$.

The R-T (or S-T) segment could be referred to simply as R-T (or S-T) or RT (or ST), with the proper subscript. It could be described as convex (curved upward), concave (curved downward), rising, or falling. Thus, $J_1 + 1$, RT_1 convex, $T_1 - 3$ would indicate, in Lead I, a take-off from the descending limb of R which is elevated 0.1 mv. above the isoelectric line, and is followed by a convex R-T segment which descends finally to an inverted T, 0.3 mv. below the isoelectric level.

FOURTH LEAD NOMENCLATURE

It is now accepted usage to designate Lead I as RL, Lead II as RF, Lead III as LF. Therefore, the chest, or fourth, lead should be designated as FC instead of CF, for, by so doing, the order of the letters would indicate that the current is running in the same direction in all four leads. This would simplify the method of application of the electrodes for technicians and for beginners in electrocardiography.

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The subscript for the various positions of the chest electrodes could be appended as needed; the description of the routine fourth lead would be FC_4.

SUMMARY

1. It is suggested that the origin, take-off, or junction (with R or S) of the R-T (S-T) segment be identified by the letter J (for junction), and that the lead be identified by the proper numerical subscript.

2. RT or ST would then be adequate to indicate the R-T or S-T segment. It could be further described as convex, concave, rising, or falling.

3. The designation of the customary chest lead should be FC, instead of CF, for FC indicates that the direction of the flow of current is the same as that in the standard three leads.

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899 MADISON AVENUE

Department of Clinical Reports

COARCTATION OF THE AORTA IN A CHILD WITH ARRESTED SUBACUTE BACTERIAL ENDARTERITIS AND A CALCIFIED MYCOTIC ANEURYSM AT THE SEAT OF STRICTURE*

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THIS is the report of an unusual case of coarctation of the aorta, in a child, complicated by subacute bacterial endocarditis and endarteritis, with the development of a mycotic aneurysm of the descending thoracic aorta at the point of constriction. Furthermore, calcification has been developing in the walls of the sac, and the child appears to have recovered from the active, infective process.

Coarctation of the aorta of the adult type may be defined as a congenital stenosis, or a complete atresia, of the descending arch at, or near, the insertion of the ductus arteriosus. It is explained, at least in many of the cases, as the result of an abnormal extension into the contiguous wall of the aorta of the obliterative process which normally takes place in the ductus in the first weeks of postnatal life. In others, it would seem to be a true arrest of development of the fourth, left, aortic arch.

The degree of the stenosis is balanced by the amount of collateral circulation which develops between the branches given off above, and those below, the constriction. Usually, all of the vessels to the head and upper extremities arise proximal to the coarctation, which produces a relative increase of the blood supply to these parts, as evidenced by marked, bounding pulsation, a ruddier color of the face, and a higher level of intelligence than the subject might otherwise have had.

The condition is not common. It occurred as a primary lesion in 7 per cent of the thousand cases of congenital heart disease analyzed by Abbott.[1] The diagnosis is based on the combination of elevated blood pressure in the upper extremities with an absent, or diminished, pressure in the lower, abnormal pulsation of the enlarged collateral vessels above, with absent femoral pulsations, and, in the roentgenogram, "scalloping" of the ribs and, frequently, absence of the aortic knob.

Since the appearance, in 1928, of Abbott's[2] classic analysis of 200 collected cases of coarctation with autopsy, this condition has become familiar to all, and no attempt will be made here to discuss in detail the clinical features or to review the literature. It is to be noted, how-

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ever, that, of these 200 cases, death was caused in fourteen (7 per cent) by an infective endarteritis, with the resultant formation of a mycotic aneurysm. The process is identical with the almost constantly fatal invasion of the heart in subacute bacterial endocarditis, in which the prominent feature is an intrusion of the infective agent, commonly the *Streptococcus viridans*, into the tissues of an already diseased or congenitally malformed valve. In this connection, it is to be noted that the aortic valve is bicuspid in a relatively large proportion of cases of coarctation (nearly 25 per cent in Abbott's 200 collected cases), and this provides a favorable nidus for the infective process. Congenital subaortic stenosis, caused by an annular, fibrous shelf lying a short distance below the valve, also may occur with coarctation, and may be the seat of bacterial invasion.

In this connection, it is interesting to recall the recent work of Kinsella and Muether,[3] who produced experimental bacterial endocarditis in dogs, both by intravenous and oral administration of *Streptococcus viridans.* Dogs with previously traumatized heart valves developed bacterial endocarditis and ran a typical clinical course, with a fatal outcome. Dogs with normal valves escaped infection. One must bear in mind that the valves in the dogs with bacterial endocarditis were damaged by trauma and not by disease. Perhaps this is the reason why sulfanilamide and merthiolate were highly successful in the treatment. It would be interesting to see what the effect of this treatment would be on reinfected, cured dogs whose valves would therefore have been damaged by disease.

Richey,[4] in a study of 41 collected cases of aneurysm of the thoracic aorta in persons under 18 years of age, found a mycotic lesion in 20, and four of the latter also had coarctation of the aorta. Because of the kinking and wrinkling of the aorta in the area immediately distal to the stricture, and the eddying of currents here, this point is commonly the site of the mycotic aneurysm. Thus, in 13 of the 14 instances of this condition which were cited above,[2] the aneurysm was at or below the seat of constriction. Rupture occurred in three of these. In one case, that of a girl of 12 years, the aneurysmal site was just distal to the constriction, and rupture took place into the left bronchus.[5] In another case, a boy, aged 10 years, had a mycotic aneurysm distal to the coarctation which ruptured into the esophagus.[6] In the third, a lad of 17 had a mycotic aneurysm 1 cm. below the constriction which ruptured into the left pleural cavity.[7]

The course in subacute bacterial endocarditis or endarteritis is long-drawn-out, and similar in many respects to any chronic infection. Rarely have recoveries from this usually fatal disease been reported. Libman says that "subacute bacterial endocarditis is a disease in which healing can occur from the bacterial, pathological, and clinical standpoints." He has witnessed seventeen spontaneous recoveries.[8] In the

present state of our knowledge, however, therapeutics offers little hope of cure. The various forms of treatment that have been tried have almost invariably proved to be unsuccessful. The newer chemotherapeutic agents may offer more hope in the future.

The case now to be presented illustrates several of the above-mentioned features.

CASE REPORT

The patient, a girl of 12 years, first visited the Children's Medical Clinic of St. Luke's Hospital in May, 1931, when she was 5 years old. She was suffering from acute tonsillitis, headache, and fever. She was fair, tall, and thin. She weighed 8½ pounds at birth; the delivery was normal. She was the third child of apparently healthy, young, Irish parents. She had had pneumonia at the age of 5 weeks, and diphtheria when she was one year old.

On physical examination, a systolic murmur, which was loudest over the right side of the base of the heart, was heard. It was then regarded as a congenital heart murmur of little clinical significance. No thrill, clubbing of the fingers, cyanosis, or dyspnea was noted. The child lived on the fifth floor and had run up and down stairs many times daily without difficulty.

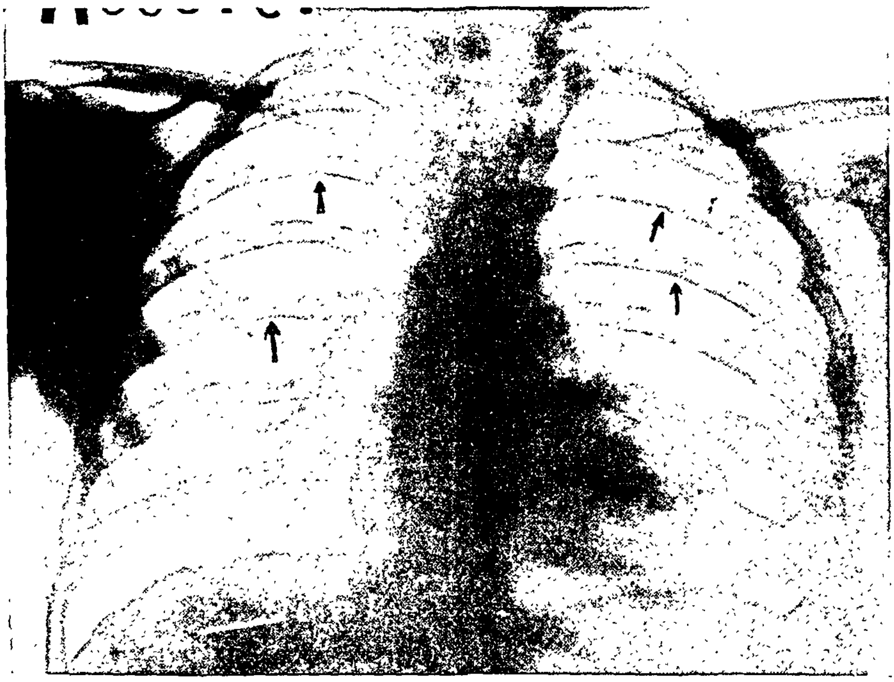

Fig. 1.—Teleoroentgenogram taken July 6, 1936, at onset of infection. Note absence of aortic knob and early notching of ribs (black arrows).

She had her tonsils removed in May, 1933, after frequent attacks of tonsillitis. She kept returning to the children's medical clinic, and it was noted that the character of the systolic murmur at the base of the heart varied somewhat; it was usually soft and low in pitch. A diagnosis of coarctation of the aorta was made when it was discovered that the blood pressure was 180/90 in the upper extremities, and 110/90 in the popliteal arteries. (Following rest, the blood pressure dropped to 140/90 in the brachial arteries and could not be measured in the popliteal arteries.) Forceful brachial pulsations were present, but there were no femoral pulses. Intercostal arterial pulsations were palpable. The retinal

vessels were tortuous and pulsating. Slight notching of the ribs and absence of the aortic knob were noted in the teleoroentgenogram (Fig. 1). Polygraphic tracings of the radial and femoral pulses showed that the femoral pulse was smaller and had a slow rise and fall (Fig. 2).

On July 3, 1936, the child, then 10 years old, came to the clinic complaining of precordial pain, fever, and headache. A loud, rumbling, systolic murmur of a different character was heard over the aortic area and the back, and the spleen was palpable. The child was admitted to the ward for observation because it was thought that she might have subacute bacterial endocarditis engrafted upon a subaortic stenosis or congenitally bicusped aortic valve.

On admission, the temperature ranged between normal and 103° F. The hemoglobin was 50 per cent. The erythrocyte sedimentation rate was 80. The leucocytes numbered 16,000, of which 78 per cent were polymorphonuclears. Two weeks after admission, a tender, red spot appeared on the plantar surface of the terminal phalanx of the left toe, became purple, and disappeared in a few days. This was the first of many embolic phenomena which occurred during the period between July, 1936, and February, 1937. Petechiae also appeared frequently, mostly on the lower extremities. The child was pale, and a secondary anemia, with a hemoglobin of 50 to 60 per cent, continued for several months. Serial electrocardiograms showed that left axis deviation, which had not been present in 1931, was developing.

On July 23, twenty days after admission, the blood culture was positive for *Streptococcus viridans*. The culture was again positive for the same organism on August 6.

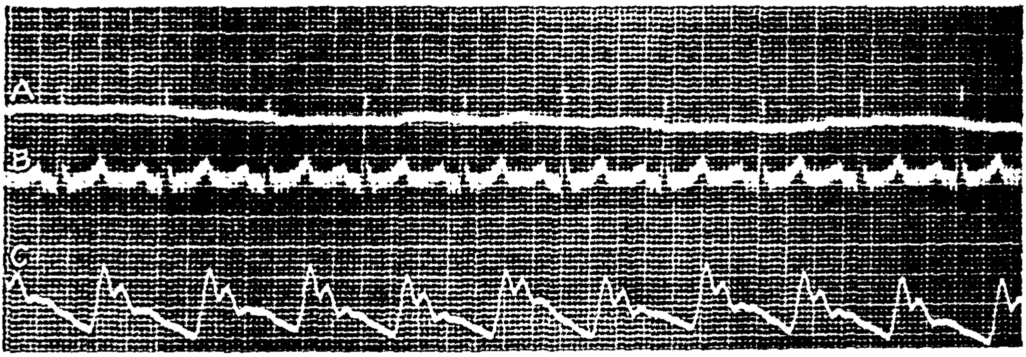

Fig. 2.—Polygraphic tracings taken simultaneously with electrocardiogram. *A*, Femoral curve is extremely low, and the start of the wave is slightly later than that of the radial. *B*, Lead I of electrocardiogram, showing no abnormality. *C*, Radial pulse tracing.

On July 24, severe pain occurred in the left upper quadrant of the abdomen, and the spleen became extremely tender. This was thought to be caused by splenic infarction. This complication recurred on August 13 and October 8. On November 7 there was severe pain in the left kidney region, followed by hematuria. These symptoms were indicative of infarction of the left kidney.

A teleoroentgenogram which was made September 5, two months after admission, showed a new shadow in the area of the pulmonary artery. In the left anterior oblique view this was seen to be in the position of the descending portion of the arch of the aorta. The barium-filled esophagus was displaced to the right.

During this time the child was treated symptomatically. She was given five blood transfusions, of 250 c.c. each, by the direct method. Codeine and other sedatives were used to relieve pain. She was put on a high-caloric, high-vitamin diet, and received ultraviolet irradiation at regular intervals throughout her illness.

Toward the end of December, 1936, a change was noted in the temperature curve. The high peaks no longer occurred. On February 5 the temperature was

normal, and the child became symptom-free. During the spring and summer of 1937, she was carefully watched for signs of latent subacute bacterial endocarditis. However, she has had no recurrence of fever or other symptoms from that time to date, an interval of two years. At the present time the child appears well and happy. She has a home teacher, with whom she is progressing rapidly. She has gained satisfactorily in weight and in height, and has no symptoms referable to her heart disease.

The teleoroentgenogram which was made in January, 1939 (Fig. 3), showed fine white lines of calcification around the periphery of the aneurysm. (These began to appear in the roentgenogram sixteen months after admission.) The left ventricle was enlarged, and the size of the aneurysmal shadow had increased slightly. The "scalloping" of the ribs was more marked than on earlier examinations.

SUMMARY

A case of subacute bacterial endocarditis and endarteritis, with apparent recovery, is reported in a child who has coarctation of the aorta of the adult type, and now, as a result of the endarteritis, has a mycotic aneurysm, with calcification of its walls, which is situated in the descending arch, apparently at the seat of the coarctation.

ADDENDUM

Since the above observations were made, the chambers of the patient's heart and her great vessels have been visualized by a radiopaque substance, diodrast. This procedure[9] was carried out by Dr. George P. Robb and Dr. Israel Steinberg, to whose courtesy I am indebted for the following illustrations: Figs. 4, 5, 6, *7A* and *7B*. (The overlay tracing and the legends were made by Dr. Ursula Roche and Dr. Stewart F. Alexander.)

The operation was simple and unaccompanied by any untoward reaction. There was a preliminary fluoroscopic examination to find preferred angles of the heart, and also an accurate measurement of the circulation time (to ascertain the time required to fill the right and left sides of the heart). The child was then held in place before the screen by wide straps, and diodrast was rapidly injected into the raised arm through the median basilic vein. Films were taken in rapid succession at predetermined intervals. The patient complained of a sensation of heat during the injection, and had some allergic reaction, as evidenced by swelling of the lips. However, the symptoms must not have been very serious, for half an hour later the child ate a very substantial lunch.

I should like to draw special attention to the work of these investigators. I feel that this method opens a new chapter in the study of congenital heart disease. Anatomic abnormalities of the heart or great vessels, when accurately visualized in this way, may become amenable to surgical correction. In the case presented herewith, the possibility of wiring, ligating, or even removing the aneurysm suggests itself, since it might prevent rupture of the aneurysm and sudden death.

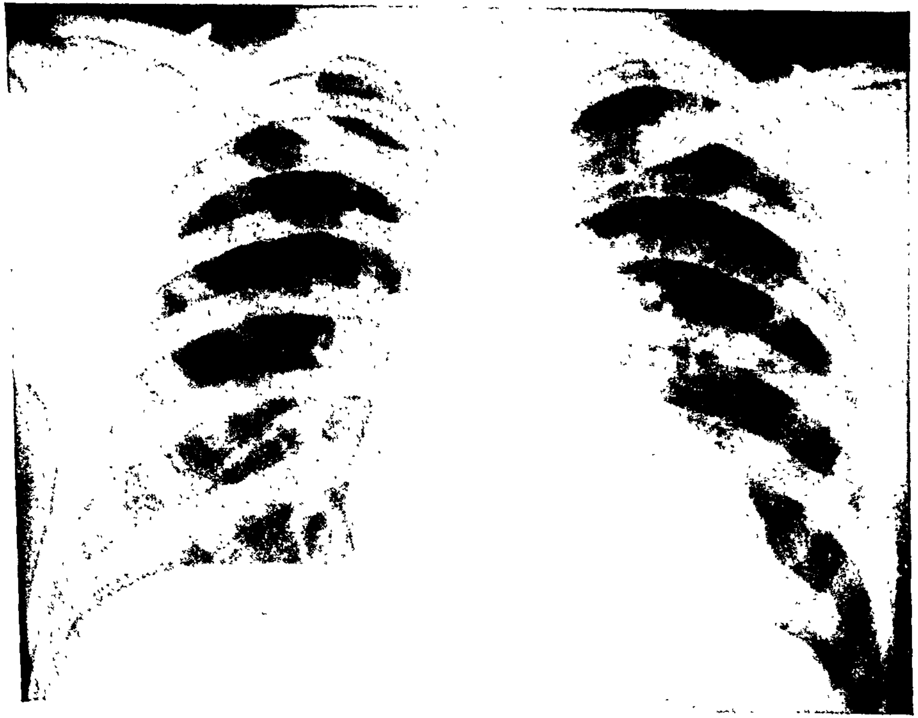

Fig. 3.

Fig. 4.

Fig. 3.—January, 1939. Posteroanterior view, showing enlarged left ventricle, above which extends the convex shadow of the aneurysm. Note areas of calcification in the periphery of the aneurysm. Compare with contrast films, Figs. 4 and 5.

Fig. 4.—Contrast roentgenogram. Posteroanterior view taken 3 seconds after beginning of injection of opaque substance. The right-sided chambers of the heart are outlined. The right axillary, subclavian, and innominate veins, the superior vena cava, the right ventricle, and the pulmonic artery, with its right and left branches and arborizations within the lungs, are clearly seen. Black arrow indicates interventricular septum. Note that the aneurysmal shadow is not filled, and lies outside the pulmonary artery.

Fig. 5.

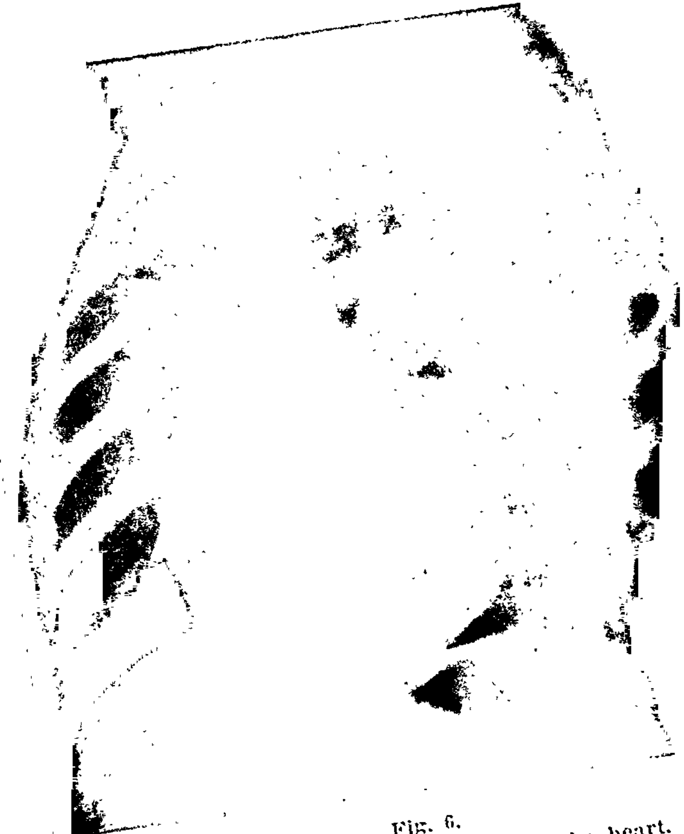

Fig. 6.

Fig. 5.—Contrast roentgenogram. Posteroanterior view taken 8 seconds after injection, showing filling of the left side of the heart. The left ventricle and descending aorta and the aneurysm are filled with contrast medium. Note the thickness of the left ventricular wall, the dilated left subclavian artery, and the collateral arterial circulation over scapulae.

Fig. 6.—Conventional roentgenogram. Left anterior oblique position. Note poor definition of supracardiac vascular structures, enlargement of left ventricle, and aneurysmal shadow posterior to bifurcation of the trachea. The left bronchus appears to be displaced anteriorly and downward by the aneurysm. Note the shadow of the ligamentum arteriosum, which is seen, in this and the succeeding illustrations, as a band extending from the pulmonic artery to the aneurysm. It does not fill with contrast medium, and is constantly present in this case.

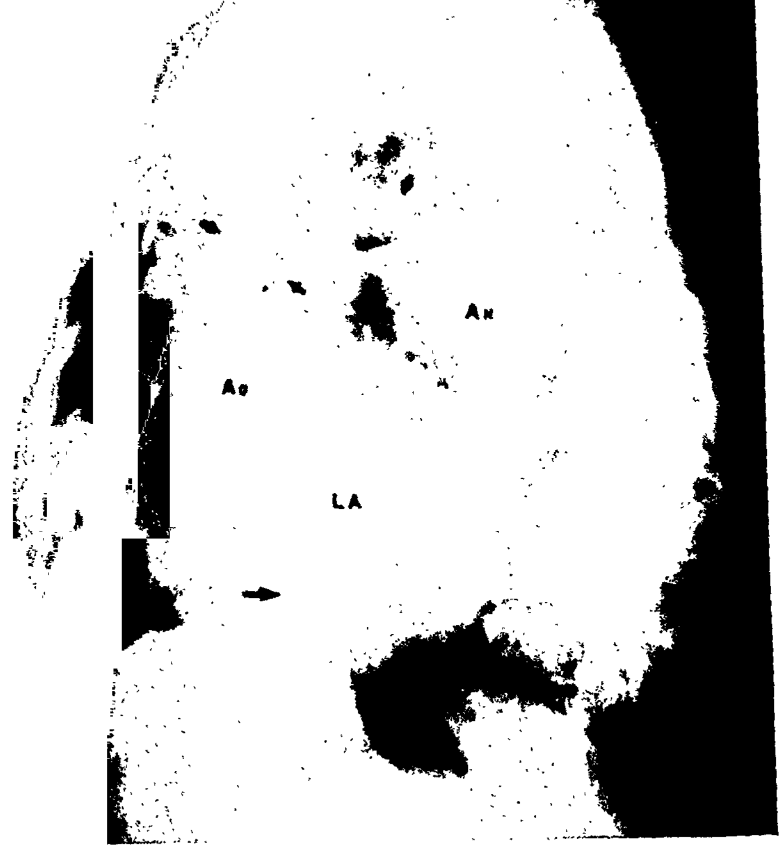

Fig. 7A.

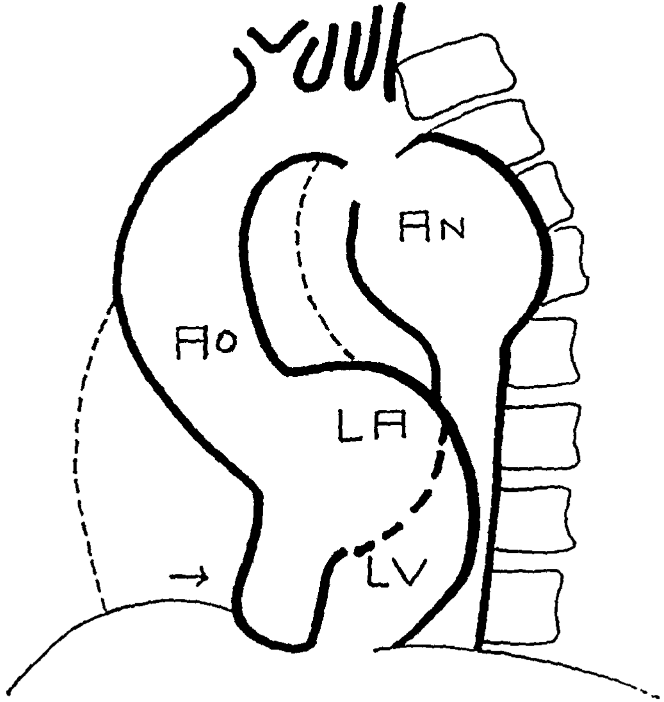

Fig. 7B.

Fig. 7A.—Contrast roentgenogram. Left anterior oblique view, 8 seconds following the injection. The left auricle, the left ventricle, and the aorta are visualized. The left ventricle is indistinct, as if in early diastole. Lowest black arrow denotes the interventricular septum and, probably, stream of blood entering left ventricle from left auricle. The intercardiac origin of the aorta is clearly seen. The ascending aorta is dilated, but the arch shows progressive narrowing to a point just beyond the origin of the left subclavian artery, where the maximal constriction is noted (upper left arrow). Immediately below this, the aneurysm is clearly outlined, and the contrast medium is seen entering the descending aorta.

Fig. 7B.—*LA*, left auricle; *LV*, left ventricle; *Ao*, aorta; *An*, aneurysm. Note branches to neck from arch of aorta. Arrow indicates interventricular septum and stream of blood flowing into left ventricle.

Surgical intervention, however, in a child whose present condition appears to be excellent is certainly to be approached with caution.

I wish to thank Dr. Maude E. Abbott and Dr. F. Elmer Johnson for valuable suggestions.

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ORTHOSTATIC PAROXYSMAL AURICULAR TACHYCARDIA WITH UNUSUAL RESPONSE TO CHANGE OF POSTURE

Report of a Case

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An attack of paroxysmal auricular tachycardia may occasionally be precipitated or terminated by certain changes of posture. The heart rate when a paroxysm is in progress, however, is affected inappreciably, if at all, by change of posture.[1] So rigid is this rule that an exception may be regarded as a curiosity.

We are prompted to report the following case because it is remarkable in two respects. Over a period of two years, unless it was prevented by digitalis or quinidine therapy, paroxysmal auricular tachycardia occurred invariably when the patient assumed the sitting or standing position. Of perhaps greater interest was the marked response of the rate of the tachycardia to change of position.

CASE REPORT

O. H., a 16-year-old white schoolgirl, was referred to the Cardiac Clinic of the Newark City Health Department in October, 1937, because of tachycardia. Since 1931 she had experienced recurrent attacks of pain and swelling of the joints of undetermined etiology. The knee, elbow, and wrist joints were involved symmetrically. In July, 1935, she was found to have prenatal syphilis, and appropriate therapy was instituted.

The chief complaint was abnormal fatigability. There were but slight dyspnea and palpitation on unusual exertion or excitement. For several years she had noticed weakness, dizziness, and, occasionally, syncope, upon standing erect. These symptoms were particularly annoying when she arose from bed after a sleep. Headaches occurred very frequently. She practically never perspired, and was greatly distressed by hot weather. The menses were scant and irregular, and there was moderately severe dysmenorrhea.

Her father was suffering from syphilis and pernicious anemia. Her mother and sister also had syphilis. A brother had died of acute appendicitis.

Physical Examination.—The patient was a fairly well-developed adolescent girl of average intelligence. She weighed 104 pounds and was 4 feet 10.5 inches tall. There was no abnormal pigmentation of the skin or mucous membranes.

The pupils were irregular, unequal, slightly dilated, and reacted sluggishly to light. The upper central incisors were typical Hutchinson's teeth. The tonsils were not obviously diseased. The thyroid gland was not enlarged. The thoracic contour and the lungs were normal. The apex beat was within normal limits. No thrills or abnormal pulsations were present. The heart rate (seated) was 180 per minute, and the beating was regular. The heart sounds were normal at the apex, but the pulmonic second sound was split. No murmurs were audible. The blood pressure was 80 (?) mm., systolic, and 60, diastolic.

From the Cardiac Clinic, Newark Health Department, Newark, N. J.
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No abdominal organs or masses were palpable. The kneejerks were hyperactive.

Laboratory Data.—The erythrocytes numbered 4,710,000, and the hemoglobin was 90 per cent. The leucocyte count was 9,500, and the differential count showed 74 per cent polymorphonuclear leucocytes, 22 per cent lymphocytes, 2 per cent eosinophiles, 1 per cent basophiles, and 1 per cent monocytes. The urine was normal. The blood sugar level was 80 mg. per 100 c.c., and the blood urea, 14 mg. per 100 c.c.

The blood Wassermann reaction was strongly positive (4 plus). Examination of the spinal fluid gave the following results: Wassermann reaction, anticomplementary; globulin, positive; cell count, 7; colloidal gold curve, 5555320000.

On three occasions the basal metabolic rate was −25 per cent, −26 per cent, and −13 per cent, respectively. The Mantoux tuberculin reaction was negative with 0.1 c.c. of 1:100 O. T. The vital capacity was normal (2,900 c.c.).

A teleroentgenogram showed a hypoplastic type of heart. Roentgenograms of the knee joints showed nothing abnormal.

Electrocardiograms which were taken shortly after admission showed a heart rate of 150 per minute. The auricular complexes were indistinguishable because they were fused with the T waves. At this time, these tracings were thought to show sinus tachycardia.

Additional Cardiovascular Studies.—During the past two years the patient has reported for examination more than sixty times. When she was not taking an adequate amount of digitalis or quinidine, she invariably had a marked tachycardia, which was of particular interest because of its response to change of posture. For example, the pulse rate was usually about 120 per minute in the recumbent position, 150 in the sitting and 180 in the standing. The range in pulse rate in the recumbent position was from 80 to 140, in the sitting, from 108 to 180, and in the standing, from 136 to 200 per minute. The difference between the recumbent and standing rates was never less than 40 beats per minute, and the rate in the sitting position was usually about the mean of the other two.

The heartbeat was always regular when she was in the erect posture. Rarely, dropped beats were noted when she was in the sitting position. The heartbeat was most often irregular during recumbency. Elevation of the foot of the bed accentuated the irregularity and retarded the pulse rate.

The change in pulse rate when the patient passed from the horizontal to the vertical position was instantaneous. When she changed from the vertical to the horizontal, however, the alteration in rate was sometimes abrupt, and sometimes gradual.

The pulse rate was accelerated by exercise only on the rare occasions when the rate in the erect posture was below 150 per minute. When the patient was standing, the application of oculobulbar or carotid sinus pressure did not retard the pulse rate or restore normal rhythm. There was no response to the Valsalva experiment.

It was possible, by administering digitalis or quinidine, to maintain the pulse rate at a normal level, i. e., about 90 per minute in the supine, and 96 in the standing, position.

The blood pressure was usually between 90 and 100 mm. Hg, systolic, and 60 and 75, diastolic. Its postural variations, however, were within normal limits (Table I). The blood pressure was not significantly altered by digitalis or quinidine. The application of a tight abdominal binder did not influence the blood pressure or pulse rate.

Analysis or Electrocardiograms.—Electrocardiograms which were taken in the erect posture on five occasions showed paroxysmal auricular tachycardia. On June 29, 1939, the rate was 162 per minute and practically constant (Fig. 1). The P wave was inverted in Lead I and upright in Leads II and III. The ectopic focus was therefore thought to be located in the left auricle.[2] The P-R interval

was normal. There was electrical alternation of the QRS complexes in all leads, and of the T wave in Lead IVF.

In the sitting position the heterotopic rhythm persisted, although at a considerably slower rate (Fig. 2). Minor differences in the contour of the P waves, as compared to those in Fig. 1, were noted, but were ascribed to the postural change rather than to a shift of the pacemaker. The rate was not constant; it varied from 130 to 144 per minute. On other occasions, when the rate in the sitting position was more rapid, minor degrees of electrical alternation were observed.

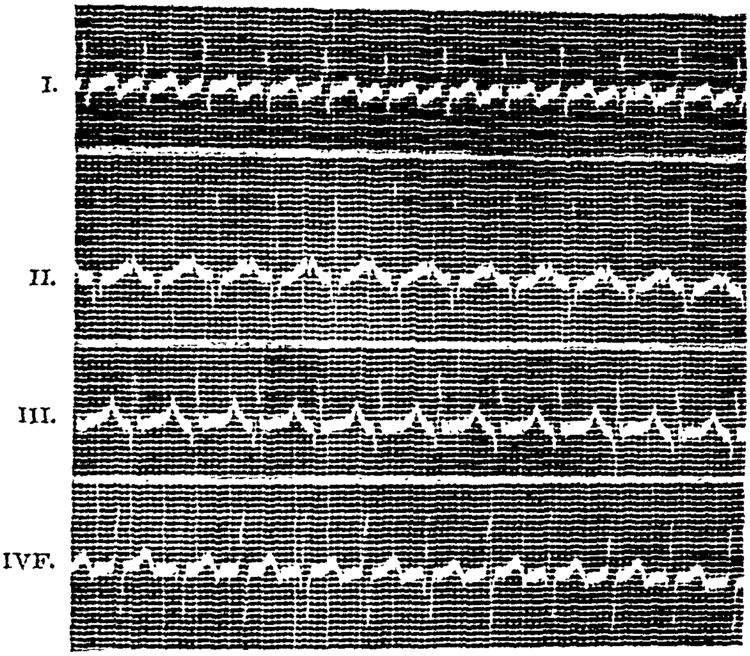


Fig. 1.—Electrocardiograms taken June 29, 1939, with the patient standing. Paroxysmal auricular tachycardia; rate, 162 per minute. P wave inverted in Leads I and IVF. Electrical alternation of Q_1, R_1, S_1, Q_2, R_2, Q_3, Q_4, R_4, S_4, and T_4.

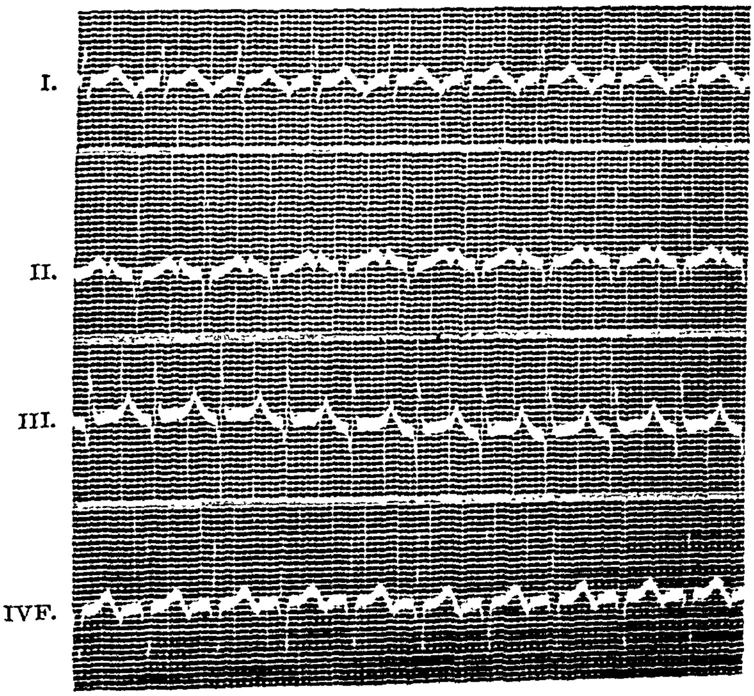


Fig. 2.—Electrocardiograms taken immediately after those in Fig. 1, with the patient sitting. Rate reduced and inconstant, varying from 130 to 144 per minute.

TABLE I

SELECTED RECORDS OF PULSE RATE AND BLOOD PRESSURE IN SUPINE, SITTING, AND STANDING POSITIONS

DATE	PULSE			BLOOD PRESSURE					
				SUPINE		SITTING		STANDING	
	SUPINE	SITTING	STANDING	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
7/ 7/38	100	128	160	98	70	96	70	90	75
7/ 8/38	120	180	180	95	60	90	70	90	70
7/14/38	120	150	180	105	60	98	70	90	75
9/27/38	140	160	200						
2/14/39	80	136	136						
4/27/39	80	108	150	96	60	95	64	88	65
5/11/39	138	150	180	96	68	88	70	86	70
6/20/39	88	140	160	100	60	96	60	94	70
8/23/39	80	150	186						

When the patient was recumbent, the following variations in the behavior of the rate and rhythm occurred at different times:

1. Normal sinus rhythm was restored (Fig. 3).

2. The auricular tachycardia persisted, but at a slower rate than in the sitting or standing position. Thus, on July 13, 1938, the rate when she was standing was 188 per minute, when she was sitting, 150, and, when she was recumbent (Fig. 4), it was between 120 and 125.

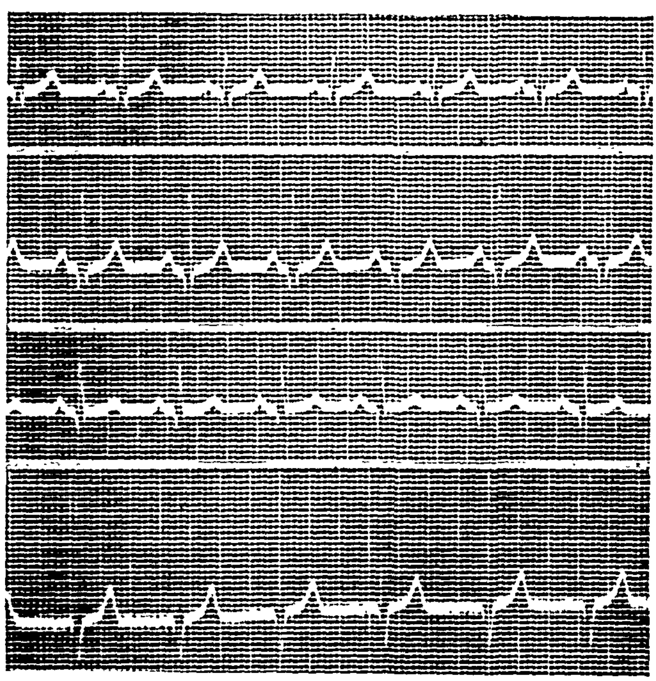
I.
II.
III.
IVF.


Fig. 3.—Electrocardiograms taken immediately after those in Fig. 2, with the patient supine. Normal sinus rhythm; rate about 90 per minute.

3. There were repeated, short runs of paroxysmal auricular tachycardia, interrupted by isolated beats of sinoauricular origin. During the runs of tachycardia, incomplete auriculoventricular block, with Wenckebach's phenomenon, occurred. The auricular complexes appeared to be polymorphic. We believed that this was caused by differences in points of incidence of the P waves upon the preceding T waves,

rather than by an actual shift of the pacemaker. The T waves showed interesting variations in amplitude (Fig. 5).

COMMENT

As far as we have been able to ascertain, this case, in which paroxysmal auricular tachycardia invariably occurred when the upright position was assumed, is unique. The only comparable case in the literature is that of Sanders,[3] in which orthostatic tachycardia accompanied orthostatic hypotension. The pulse rate doubled abruptly when the patient changed from the supine to the standing position, and this increase was approximately halved when he assumed the sitting position. Pulse irregularities were observed at times, but their character was not ascertained. However, Sanders did not definitely classify the tachycardia, and his electrocardiographic studies were not complete.

Since the exact mechanism of the production of paroxysmal auricular tachycardia remains unknown, any attempt to explain its constant occurrence as an orthostatic phenomenon is necessarily a matter of sheer speculation. Local changes in excitability caused by inadequate blood supply to the myocardium may be a factor of importance. In this connection, Akesson[4] demonstrated in instances of orthostatic arterial ischemia that the T wave was negative and the S-T segment depressed; these changes are regarded as a result of myocardial anoxemia. More logically, perhaps, the explanation is to be found in changes in the activity of the extrinsic cardiac nerves.

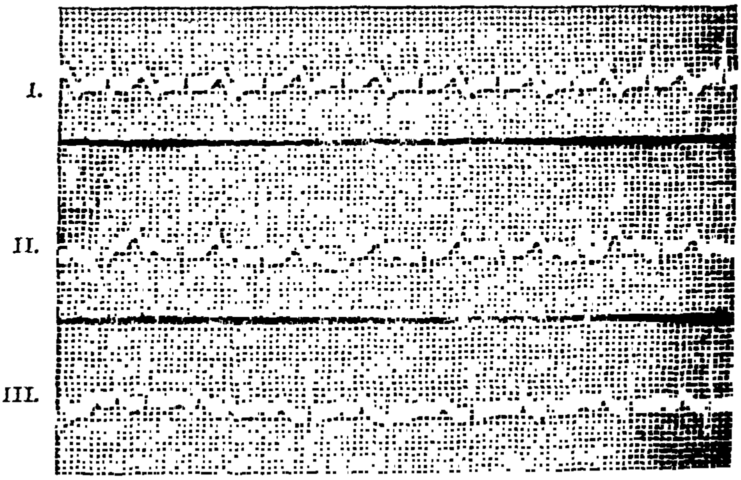


Fig. 4.—July 13, 1938. Supine position. Paroxysmal auricular tachycardia; rate, 120 to 125 per minute.

It is generally accepted that assumption of the supine position increases the vagal tone. This is caused by the increased flow of blood to the head, which results in stimulation of the vagal centers, either directly or reflexly, by way of the carotid sinus. In the upright position, on the contrary, there is a tendency toward massing of blood in the splanchnic area and lower extremities, and, consequently, vagal activity is indirectly lessened.[5]

There is considerable evidence that the onset of paroxysmal auricular tachycardia may coincide with sudden diminution in vagal tone. The attacks which follow fright, anger, excitement, and other emotions are probably to be attributed to this factor. Galli[6] succeeded in precipitating paroxysmal auricular tachycardia in a patient by the administration of atropine. Otto and Gold[7] had a similar experience with epinephrine. Graber[8] observed an interesting case of Hodgkin's disease in which frequent attacks of paroxysmal auricular tachycardia occurred. At autopsy, the vagi were found to be degenerated as a result of pressure by enlarged mediastinal lymph nodes.

Fig. 5.—Oct. 13, 1938. Patient supine. Normal auricular complexes designated *P*; ectopic complexes, *P'*. Short runs of paroxysmal auricular tachycardia, during which there are incomplete A-V block, with Wenckebach's phenomenon, and variations in the amplitude of the T waves.

It may be assumed that, in our case, a potential ectopic focus becomes activated in the erect posture as a result of diminished vagal activity. We do not believe that the theory of parasystole[9] is applicable, for

reference to Fig. 5 will demonstrate that the longer intervals between ectopic P waves are not exact or approximate multiples of the shortest P′-P′ intervals.

Theoretically, the nonspecialized auricular tissue is under only partial nervous control. Although the onset or termination of an attack of paroxysmal tachycardia may be related to changes in the activity of the vagus, the heart rate in a given paroxysm remains remarkably constant, and does not respond to stimuli which influence the normal sinus rhythm. Rarely, there are exceptions to the rule. Iliescu and Sebastiani[10] reported a case in which conspicuous slowing of the rate occurred during quinidine therapy. Maddox[11] described a case of paroxysmal tachycardia (possibly nomotopic) of exceptional duration and gradual decline, in which the heart rate responded to some extent to rest, exercise, emotions, and sleep. In our case, the heart rate during the tachycardia varied with posture and rarely with exercise.

It is possible that, in these exceptional cases, there is either a difference in the nerve distribution to the auricle, or an anomaly of the tissue comprising the ectopic focus, so that it possesses properties approaching those of the sinus node itself. Rothberger and Sachs[12] believe that islets of sinoauricular tissue might occur in the left auricle, which would account for some instances in which this structure exhibited automatism. Indeed, Segre[13] claimed to have traced sinoauricular nodal tissue into the left auricle.

The fact that the tachycardia rate is slower in the sitting position than in the standing position is probably the result of reflex stimulation of the vagus by afferent impulses from the lower extremities.[5] Further diminution of the rate, or termination of the paroxysm when the patient lies down, may be caused by stimulation of the carotid sinus or vagal centers by the increased flow of blood to the head.

The presence of incomplete A-V block during runs of tachycardia in the recumbent position is also to be considered as a manifestation of enhanced vagal tone. Alexander and Bauerlein[14] and Santucci[15] described cases of clinostatic heart block which they attributed to vagal influences.

Electrical alternation is an indication that the heart is overtaxed. In paroxysmal auricular tachycardia this may be caused by shortening of the diastolic rest period.[16] The occurrence of electrical alternation in our case in the erect posture, and in the sitting position only when the pulse rate was very rapid, is to be explained in this way.

SUMMARY

A bizarre case is reported, in which paroxysmal auricular tachycardia invariably occurred in the sitting or standing positions, unless held in abeyance by digitalis or quinidine therapy.

The rate of the tachycardia changed with change of position. The rate was slower in the sitting than in the standing position, and, unless normal sinus rhythm were restored, it was further reduced by recumbency. The heart rate was accelerated, on rare occasions, by exercise, but did not exhibit other sinus reactions.

Frequently, there were short runs of paroxysmal auricular tachycardia in the recumbent position, during which incomplete A-V block, with Wenckebach's phenomenon, occurred.

Electrical alternation was noted during the tachycardia in the erect position, and to a lesser degree in the sitting position when the rate was *sufficiently rapid.*

We are deeply indebted to the numerous cardiologists who reviewed this case with us and helped us to reach a solution of a most intricate problem.

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12. Rothberger, C. J., and Sachs, A.: Rhythmicity and Automatism in the Mammalian Left Auricle, Quart. J. Exper. Physiol. 29: 69, 1939.
13. Segre, R.: Quoted by Rothberger and Sachs.[12]
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15. Santucci, G.: Su due casi di blocco cardiaco parziale clinostatico, Cuore e circolaz. 16: 441, 1932.
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Department of Reviews and Abstracts

Selected Abstracts

Piccione, Frank V., and Scherf, David: The Rhythmic Formation of Coupled Beats and Paroxysmal Tachycardias in the Outer Layers of the Myocardium. Bull. New York Medical College 3: 83, 1940.

The application of hypertonic solutions of sodium chloride or barium chloride on the ventricular surface of dog hearts in situ causes extrasystolic allorhythmias and tachycardias which disappear within a few minutes. The same irregularities may be initiated with greater regularity by subepicardial injection of small quantities of the same salt solutions.

The structure of the barium tachycardias differs slightly from that of the sodium chloride tachycardias.

The rate of the tachycardias is increased by faradic stimulation of the left and especially the right stellate ganglion. Stimulation of the right or left vagus reinstitutes a tachycardia which has already disappeared or facilitates its appearance. The rate of a tachycardia appearing during and after vagus stimulation may be higher than that of the prevailing sinus rhythm.

Application of the same salt solutions to the sinus node tissue and auricular muscle bundles causes similar disturbances of rhythm. They are, however, remarkably rarer.

Even when fifteen active stimuli-forming centers were created at the same time by injections of barium chloride subepicardially, ventricular fibrillation never appeared.

Potassium chloride inhibits the formations of extrasystoles; they are rare after administration of solutions of calcium chloride.

The experiments prove the possibility of a rhythmic stimulus formation in the outer layers of the myocardium. They speak against the existence of a reentry mechanism as the cause of the extrasystoles and tachycardias, under the conditions described in this report.

AUTHORS.

Ernstene, A. Carlton: Common Errors in Diagnosis of Heart Conditions. Ohio State M. J. 36: 497, 1940.

Errors in cardiac diagnosis may be made either (1) by attributing symptoms to organic heart disease when no heart disease is present, or (2) by failing to recognize the cardiovascular origin of the patient's complaints. Mistakes of the first kind often result from incorrect interpretation of precordial pain or from failure to distinguish between true dyspnea and sighing respiration. Certain abdominal and intrathoracic conditions at times give rise to symptoms highly suggestive of coronary artery disease, and in a small group of patients with hyperthyroidism, cardiovascular symptoms and signs may so dominate the clinical picture that a diagnosis of some form of primary heart disease is made. The second kind of mistake most commonly results from failure to remember that gastrointestinal symptoms may overshadow all other complaints in certain cases of congestive myocardial failure or coronary artery disease. Less frequently, the

error results from overlooking significant physical findings in cases of valvular heart disease, chronic compression of the heart, or coarctation of the aorta, or from failure to appreciate the significance of the early symptoms of subacute bacterial endocarditis. The avoidance of these various errors depends upon thorough physical, roentgenologic, and electrocardiographic examination, and to an even greater extent upon careful analysis of the patient's symptoms.

AUTHOR.

Goetz, Robert H.: Plethysmography of the Skin in the Investigation of Peripheral Vascular Diseases. Brit. J. Surg. 27: 506, 1940.

The author gives in detail the guiding principle and the detail of construction of different types of plethysmographs, together with the interpretation of the plethysmogram.

NAIDE.

Berk, J. Edward: Circulation Time (Magnesium Sulphate Method) in the Diagnosis of Peripheral Vascular Disease. Am. J .M. Sc. **199**: 505, 1940.

Through intravenous injection of 5 c.c. of 10 per cent magnesium sulfate solution, the arm-to-tongue and arm-to-extremity circulation times were determined upon 200 normal subjects and twenty-one patients in the general classification of peripheral vascular disease.

In general, individuals with peripheral vascular disease revealed a tendency toward a longer circulation time and a higher percentage of "blank" and "persistent blank" reactions. However, wide variations were obtained both in the normal and in the abnormal groups, and even in the same individual. Thus this method cannot be recommended for testing the efficiency of the peripheral circulation of a given patient.

SCHWARTZ.

Jacobson, Edmund: Variation of Blood Pressure with Brief Voluntary Muscular Contractions. J. Lab. and Clin. Med. **25**: 1029, 1940.

Experiments are conducted on eleven subjects with normal blood pressure and on four with chronically high blood pressure, all of whom relax at least fairly well upon request, whether through special training or otherwise. Electrical measurements are taken of contraction (action potentials) in various muscle groups, while blood pressure is recorded at certain times from the left upper arm.

In an individual otherwise relaxed, successive contraction of a muscle group or groups (for example, clenching one fist), for periods of several minutes or more, and then relaxing completely for similar periods, is frequently accompanied by corresponding rises and falls of systolic and diastolic pressures. The extent of the relative rise and fall depends not only upon the intensity of the particular voluntary contraction but also upon the degree and extent of relaxation present in the general musculature. No contrasting rise in pressure may be evidenced if the patient is not well relaxed before he clenches his fist. The addition of marked contraction in other regions (e.g., if he contracts muscles in the lower limbs or elsewhere at the same time as he clenches his fist) promotes further rise in blood pressure.

Under the conditions of the experiment, it is evident that emotional factors are reduced to a minimum or absent altogether. At the very least it seems safe to say that no more emotion is present when the subject clenches his fist or stiffens his legs than when he tries to relax. Evidently, therefore, emotional variations do not account for the variations in pressure which correspond with variations in

skeletal muscle contraction. The indications are that progressive tension in a muscle group tends to elevate systolic and diastolic pressures, and that this tendency increases if contraction spreads to other groups. Accordingly, the present findings lend further support to the view that in individuals with normal, as well as with increased pressure (essential hypertension), the pressure levels at any instant vary to an important and determinable extent with the magnitudes of contraction in the various skeletal muscles.

AUTHOR.

Hiestand, W. A., Ramsey, Helen J., and Hale, Doris M.: The Effects of Cigarette Smoking on Metabolic Rate, Heart Rate, Oxygen Pulse, and Breathing Rate. J. Lab. and Clin. Med. 25: 1013, 1940.

Cigarette smoking caused an increase in metabolic rate in 82 per cent of thirty-nine subjects. In 13 per cent a decrease occurred. In 5 per cent no immediate effects were observed. The average effect on metabolic rate was an increase of 8.9 per cent. The maximum effect on basal metabolism of smoking one cigarette was reached immediately in some cases, and was delayed as long as forty-five minutes in others. The first rise in metabolic rate was typically followed by a second increase, reaching its summit about forty-five minutes later.

Smoking caused an increase in heart rate in 72 per cent of the persons, a decrease in 26 per cent, and no change in 2.5 per cent. After fifteen minutes the heart rate became slower than normal. The rate of breathing decreased immediately after smoking, returning to normal in about forty-five minutes. Smoking caused an immediate reduction in the oxygen pulse value, followed by an increase for at least forty-five minutes.

Greatest physiologic effects of smoking were shown by confirmed smokers who inhaled the smoke, and by persons who were unaccustomed to smoking. In this study, women showed more marked changes than men. More marked changes occurred in persons in a basal metabolic condition than in persons in a nonbasal metabolic condition.

AUTHORS.

Leibel, Bernard: Peripheral Circulation by Photo-Electric Recording. Brit. Heart J. 2: 141, 1940.

An instrument for recording vascular changes in the tissues of the extremities and of the body surface has been described. Calibration has been made possible by the introduction of a photometer circuit; results are therefore both qualitative and quantitative. In addition an accurate estimation of the pulse velocity may be made by superimposing the electrocardiogram on the tissue circulation record.

The amplifier circuit described is relatively free from electrical distortion and mechanical and physical artifact have been controlled by adequate insulation. The instrument is self-contained and readily portable, and records may be taken without any previous preparation of the patient.

A series of typical records has been presented and briefly described. Some of these illustrate physiologic reactions to different stimuli, such as heat, excitement, asphyxia, and vasodilatation after amyl nitrite inhalation. The remainder of the records was obtained from cases of certain cardiovascular conditions. Examples of pulsus bigeminus, pulsus paradoxus, pulsus alternans, and the Corrigan pulse have been illustrated. Comparative estimation of the circulation in each of the limbs of a patient suffering from peripheral vascular disease has been included and the effect of the "Pavaex glass boot" has been demonstrated.

AUTHOR.

Baer, Samuel, and Isard, Harold J.: The Value of the Ether Circulation Time in the Diagnosis of Right Heart Failure. Am. J. M. Sc. 200: 209, 1940.

Ether arm-to-lung circulation times were done on 329 patients.

The ether time in 184 normal patients ranged from 3.5 to 9.4 seconds, with an average of 5.8 seconds. Only six of the 184 patients had times beyond 8 seconds.

In twenty-six patients with proven pulmonary disease, the ether time ranged from 2.5 to 10 seconds. The average was 6.1 seconds, and only two of the twenty-six patients had times beyond 8 seconds.

In ninety patients with cardiac disease, the ether time ranged from 4 to 19 seconds. The average in patients without heart failure was 5.8 seconds, in those with heart failure 10.2 seconds.

The ether test is of definite value in the diagnosis of right heart failure, and its differentiation from conditions simulating right heart failure.

AUTHORS.

Kisch, Bruno, and Groedel, Franz M.: Changes in the Electrocardiogram Due to Local Cooling of the Chest Wall. Cardiologia 4: 206, 1940.

After localized cooling of certain areas of the chest-wall of the human being, the electrocardiogram shows in suitable cases (large hearts, children) typical changes. First and most distinct are those changes observed in the chest leads. Cooling of the area of the heart apex, respectively the left ventricle, leads mainly to a change in the CR V lead (s-electrocardiogram), cooling of the chest-wall over the right ventricle to a change in the CR II lead (d-electrocardiogram). The reported observations show that in the human being thermic influence upon the heart surface can cause similar changes in the electrocardiogram, just as was found in animal experiments by Bruno Kisch, L. H. Nahum, and H. E. Hoff. At the same time the correctness of the explanation of the chest wall electrocardiogram given by Franz M. Groedel is proved again.

AUTHORS.

King, E. S. J.: Regeneration in Cardiac Muscle. Brit. Heart J. 2: 155, 1940.

Examination of a recent heart wound in a young adult was undertaken to determine the possible presence of myocardial hyperplasia.

This was demonstrated by: 1. The splitting of the fibers—as indicated by the size and arrangement of the fibers and their relationship to the capillary vessels. 2. Protoplasmic outgrowths from the ends of damaged fibers. 3. The presence of double nuclei in some fibers. 4. The presence of mitotic fibers.

This does not, however, presuppose that such hyperplasia is responsible for the healing of wounds, which occurs by the usual connective tissue proliferation and by the formation of scar tissue.

AUTHOR.

van Bogaert, Adalbert, and Tombeur, A.: Scapular Atrophy and Angina Pectoris. Cardiologia 4: 121, 1940.

The following syndrome can be observed in the course of hyperalgetic anginal crises. It is characterized by continuous pain in the axilla, restriction of active and passive movements of the scapular-humeral joint, atrophy of the deltoid and, occasionally, of the biceps muscle, and osteoporosis of the head of the humerus.

This syndrome is usually found in the left shoulder where the anginal pain irradiates.

The symptoms appear in the first weeks following the angina attack, sometimes later. The osteoporosis is not due to the immobilization of the scapular-humeral joint.

Vasomotor reactions were *found on the affected side; there* is usually vasoconstriction, sometimes vasodilatation, of the large arteries.

Similar symptoms were also found in cases of gastric ulcer with radiating pain into the left shoulder, furthermore in cases of cervical arthritis (C 4—C 6) and in cases of cervical ribs.

The scapular arthropathy is explained as the result of irritation of centrifugal sympathetic fibers in the roots of C 5—C 8.

AUTHORS.

Gross, Louis: The Cardiac Lesions in Libman-Sacks Disease. With a consideration of its relationship to acute diffuse lupus erythematosis. Am. J. Path. 16: 375, 1940.

An extremely careful and detailed description of pathologic changes in the hearts of twenty-three fatal cases of disseminated lupus erythematosus is reported. Good photomicrographs are appended. The author demonstrates the presence of valvular and mural endocardial lesions typical of Libman-Sacks disease (atypical verrucous endocarditis) in at least eight cases. In all twenty-three cases lesions, which closely simulated four cases of Libman-Sacks disease, were present. Review of the literature since Libman and Sacks' paper shows clearly the clinical similarity between the disease described by them and the symptom complex which may be accompanied by cutaneous manifestations. Of Libman and Sacks' four original cases, two exhibited lupus. There is, Gross points out, a relatively acute febrile disease, often with signs of acute nephritis, often with purpura, with inflammation of the serous membranes, and with fatal outcome. At post-mortem examination, lesions of the heart similar to those described in this paper are found. These cases may or may not exhibit lupus erythematosus. His suggestion in nomenclature is that these two diseases be grouped as one and called Libman-Sacks disease. Note may be made of the presence or absence of cutaneous manifestations (disseminated lupus erythematosus). Several helpful points are listed for distinguishing this disease from certain cases of rheumatic fever and of subacute bacterial endocarditis.

STEELE.

Gardner, John W., Mountain, George E., and Hines, Edgar A., Jr.: The Relationship of Migraine to Hypertension and to Hypertension Headaches. Am. J. M. Sc. 200: 50, 1940.

Migraine occurs approximately five times as often in a group of patients who have hypertension as in a group of nonhypertensive patients of corresponding age. The association of migraine with hypertension is probably influenced by genetic factors. Some patients experience a cessation of attacks of migraine prior to or coincident with the development of high blood pressure. This seems to be related more to the advancing age of the patient than to the onset of hypertension. Individuals who no longer have migraine headaches frequently experience those of the hypertension type. Those who retain their migraine are likely to have both types severely. An individual who has migraine is more likely to experience the hypertension type of headache than one not similarly afflicted.

AUTHORS.

Dock, W.: Vasoconstriction in Renal Hypertension Abolished by Pithing. Am. J. Physiol. 130: 1, 1940.

On pithing the central nervous system of rabbits those with renal hypertension have a rapid fall of blood pressure to as low a level as normal controls. Even

holding venous pressure at high levels by intravenous infusion of acacia-Locke's solution fails to restore normal arterial pressure in these animals.

In pithed rabbits a rise in arterial pressure is easily evoked with epinephrine; the response is greater in those which have had renal hypertension for several months, but not in hypertensive rabbits nephrectomized thirty hours before pithing. No rise in venous pressure precedes the rise in arterial pressure. Renin, like epinephrine, causes a rise in arterial pressure in pithed rabbits, and thus differs from the humoral agent causing chronic renal hypertension. The latter apparently changes the reaction of the vasomotor center so as to maintain pressure at high levels. It also increases the sensitivity of the arterial response to epinephrine.

AUTHOR.

Page, Irvine H.: Demonstration of the Liberation of Renin Into the Blood Stream From Kidneys of Animals Made Hypertensive by Cellophane Perinephritis. Am. J. Physiol. **130:** 22, 1940.

Renin is liberated into the renal vein in increased amounts by the kidneys of dogs made hypertensive by cellophane or silk perinephritis, and by clamping the renal artery. Most of it disappears by the time the blood has reached the femoral artery.

Renin-activator is decreased in the blood from the renal vein and is increased in hypertensive animals when the femoral artery is reached.

Angiotonin-activator is not greatly decreased in the renal vein blood but may be increased in the femoral arterial blood in hypertensive animals.

Early in the course of malignant hypertension, large amounts of renin are liberated by the kidneys (one experiment). Later, both angiotonin-activator and renin-activator are greatly reduced or sufficient inhibitor is formed to abolish the reaction between them and angiotonin or renin (seven experiments).

AUTHOR.

Page, Irvine H.: Difference in the Activating Effect on Normal and Hypertensive Plasma on Intestinal Segments Treated With Renin. Am. J. Physiol. **130:** 29, 1940.

The reaction between renin and renin-activator is a specific one and the product of this reaction—angiotonin—causes strong contraction of isolated intestinal segments. This reaction has been employed to ascertain the renin-activating power of plasma.

Heparinized plasma derived from blood of some patients with essential hypertension causes greater renin-activation than does normal human blood. Plasma from dogs with experimental hypertension also exhibits this heightened power compared with plasma of normal dogs. This suggests that the humoral mechanism in the two types of hypertension have much in common and that the hypertensive either has increased amounts of renin-activator in the blood, or decreased amounts of renin-inhibitor, or both.

AUTHOR.

Sweeney, H. Morrow: Do the Carotid Sinuses Exert a Pressor Activity When the Systemic Blood Pressure Is Low? Am. J. Physiol. **130:** 186, 1940.

Lowering of the blood pressure in dogs anesthetized with chloralose to sustained low levels varying from 45 to 70 mm. Hg does not arouse any pressor activity in the carotid sinuses, which, if present, would be demonstrable by a fall in pressure when these areas were denervated. A gradual rise in pressure in ten of the

sixteen experiments indicates the presence of depressor activity at the time of denervation. In the other six there was no change in blood pressure.

AUTHOR.

McCann, W. S.: Chronic Pyelonephritis: A Cause of Hypertension and Renal Insufficiency. N. Y. S. M. J. 40: 400, 1940.

Seven cases are described illustrating the importance and seriousness of mild or trivial urinary infections resulting in hypertension and ultimate renal insufficiency. The disastrous effects of pregnancy in such infections and their relation to the toxemias of pregnancy are illustrated by the first case.

The importance of doing pyelographic studies in patients with "essential" hypertension is stressed. Adequate treatment of mild urinary infection by chemotherapy, as well as a search for foci of infection, to prevent sequelae is urged.

SCHWARTZ.

Reisinger, John N.: Dissecting Aneurysm of the Aorta. Arch. Int. Med. 65: 1097, 1940.

Four cases of dissecting aneurysm, with post-mortem examinations, are reported. In one case the diagnosis was made before death.

Two cases were observed for periods of three months and fourteen months, respectively. The changes present in the electrocardiograms and roentgenograms in these cases are discussed.

The absence of the typical pain of the syndrome was conspicuous in three cases, although in all cases severe symptoms developed rather abruptly.

There was severe progressive anemia in two cases.

The absence of intimal rupture in one case suggests that intramural changes may be important in the causation of dissecting aneurysms.

AUTHOR.

Hertzman, Alrick B., and Dillon, John B.: Reactions of Large and Small Arteries in Man to Vasoconstrictor Stimuli. Am. J. Physiol. 130: 56, 1940.

The possibility of synergistic participation of the large arteries in the reactions of the small arteries and arterioles supplied by them, has been studied in man, on the radial artery-digital artery field, using the photoelectric plethysmographs, previously described, to record the reactions.

The responses observed involved spontaneous waves, the reactions to a deep breath, to the breath hold, to the cold pressor test, to loud noises and various psychic stimuli.

Radial artery participation in the vasoconstriction of the finger arteries was irregular and most obvious in instances of massive disturbances of the circulation. The degree of constriction of the finger arteries had little predictive value with respect to the occurrence of constriction in the radial artery. The data appear to show selection with respect to the participation, and with respect to the intensity of the participation, of the radial artery in the vasomotor responses of the small arteries and arterioles which it supplies.

AUTHORS.

Dingle, Janet T., Kent, Gerald T., Williams, L. L., and Wiggers, C. J.: A Study of Alleged Quantitative Criteria of Vasomotor Action. Am. J. Physiol. 130: 63, 1940.

By use of simultaneous cardiometric records of the ventricles and mean arterial pressure in mildly ventilated, vagotomized dogs, data were obtained for calculating

peripheral resistance changes according to the formula $R = \frac{\text{mean pressure}}{\text{cardiac output per sec.}}$ in $\frac{\text{dynes. sec.}}{\text{cm.}^5}$, and comparing such values with the absolute and percentile changes in mean pressure.

Pressor effects on mean arterial pressure were induced in normal and "shock" dogs by reflex stimulation of the central vagus and phrenic nerves, by bilateral carotid compression, by use of epinephrine and pitressin.

The results, supported by previous tests on artificial circulation machines, strongly suggest that the quantitative estimation of changes in vasomotor tone of smaller vessels either by absolute or percentile changes in mean arterial pressures or by mathematical calculation of peripheral resistance is highly restricted even in experiments in which cardiac output is also measured. Mathematical calculations fail because mean arterial pressure, which enters into the formula, is affected by the relationship between systolic discharge and aortic capacity—but not, in our experience, by aortic elasticity. The formula does not take into account the aortic capacity in relation to systolic discharge either in the same animal or in animals of different sizes.

AUTHORS.

Bunim, Joseph J.: Lupus Erythematosus Disseminatus. Ann. Int. Med. 13: 1399, 1940.

A case of lupus erythematosus disseminatus is reported in a white American girl, aged 20 years, who was observed over a period of twenty months from onset to termination of her illness. The patient exhibited most of the numerous features of the disease and was closely observed so that a fairly complete account of the natural history of the disease in this case was developed.

Clinically this case exhibited photosensitivity, cutaneous eruption, alopecia, arthritis, pericarditis, endocarditis, petechiae, papilledema, pleuritis, pneumonitis, nephritis, transient uremia, splenomegaly, hepatomegaly, ascites, peripheral edema, gastrointestinal disturbances, prolonged fever, anemia, leucocytosis, delirium, convulsions, and coma.

The significant findings at necropsy consisted of atypical verrucous endocarditis with superimposed bacterial endocarditis, adhesive pericarditis, disseminated vascular lesions, polyserositis, focal and diffuse glomerular nephritis, and interstitial pancreatitis.

MCGOVERN.

Genzler, A. M., and Fox, T. T.: Disseminated Lupus Erythematosus a Cutaneous Manifestation of a Systemic Disease. Arch. Int. Med. 65: 26, 1940.

A well-studied case of lupus erythematosus occurring in a male, diagnosed ante mortem and confirmed by post mortem is reported. The pathologic material is presented together with photomicrographs of the characteristic lesions. The review of literature on this subject is well done.

MCGOVERN.

Finkelstein, Reuben, and Jacobi, Mendel: Dissecting Aneurysm of the Aorta With a Case Report. Ann. Int. Med. 13: 1991, 1940.

A case of dissecting aneurysm of the aorta on the basis of arteriosclerotic changes, with some ideas compiled from the literature as to etiologic factors in this condition, is presented.

SCHWARTZ.

Winternitz, M. C., and LeCompte, P. M.: Experimental Infectious Angiitis. Am. J. Path. 16: 1, 1940.

Various bacteria were introduced under aseptic technique into the adventitial tissue (more rarely on a thread into the lumen or into a doubly ligated stretch) of femoral, jugular, and carotid vessels of goats. By varying the virulence of the organism and the duration of the experiment, lesions of both artery and vein were obtained, ranging from acute suppurative and proliferative reactions with thrombosis to old, fibrous intimal plaques. A potential vascular pathway for passage of infection from vein to artery has been demonstrated in both goat and man by injection methods.

AUTHORS.

Agress, Harry, and Smith, Margaret G.: Purpura Haemorrhagica Associated With Widespread Deposits of Crystalline Material: Reticuloendotheliosis. Arch. Path. 29: 553, 1940.

A case is reported of purpura hemorrhagica in which unique changes were observed due to the presence of crystalline material in the components of reticuloendothelial system and in other unrelated tissues. It is conjectured that this anatomic picture was the result of a metabolic disturbance and the possibility that the crystalline material was protein in nature was considered.

SCHWARTZ.

Green, Harold D., and Gregg, Donald E.: The Relationship Between Differential Pressure and Blood Flow in a Coronary Artery. Am. J. Physiol. 130: 97, 1940.

The moment-to-moment rate of flow into coronary arteries was measured while the vessels were perfused under relatively constant heads of pressure.

Comparison of the rate of blood flow into a coronary artery with the differential pressure (difference between the perfusion pressure and peripheral coronary pressure) shows that: 1, the peripheral coronary pressures indicate the exact time relations of the changes of resistance to flow in the coronary arteries; 2, the systolic and diastolic values of these curves correctly represent the heads of pressure that will just not cause inflow of blood during the respective periods of the cardiac cycle; 3, the differential pressure curves represent the direction and roughly the magnitude of the phasic changes of coronary flow but underestimate the exact value of the moment-to-moment coronary flow.

The curves obtained indicate that under normal conditions (perfusion of the coronary artery with blood from the aorta) the intramural blood flow will show a sudden retardation with the onset of isometric contraction, during systole forward flow will persist in most hearts, with the onset of isometric relaxation forward flow will rapidly increase and will remain rapid during the latter part of diastole diminishing slightly with the decline of the head of pressure in the aorta.

AUTHORS.

Gregg, Donald E., and Green, Harold D.: Effects of Viscosity, Ischemia, Cardiac Output and Aortic Pressure on Coronary Blood Flow Measured Under a Constant Perfusion Pressure. Am. J. Physiol. 130: 108, 1940.

The effects of several altered circulatory conditions on coronary flow have been studied during perfusion of the coronary artery with blood under a constant head of pressure. We have confirmed previous findings (using the method of differential pressures) that in elevation of blood pressure and increased cardiac output following augmented venous return, the coronary bed receives an increased

blood supply because, although the aortic pressure rises, the peripheral coronary pressure fails to rise as much. However, the increase of flow which actually occurs is generally somewhat greater than that predicted from the differential pressures.

In addition, the reduction in viscosity of the perfusate by substitution of Locke's solution for blood causes an unexpectedly large increase of flow—amounting at times to 300 to 400 per cent of the rate observed with blood. Also, a period of ischemia of the coronary bed greatly increases the flow during the initial period of restored circulation. Such flow augmentations are suggested by the concomitant slight decrease in peripheral coronary pressure, but the method of differential pressures fails to indicate the magnitude of the flow change.

It is concluded that peripheral coronary pressure curves can accurately represent the time relations of the change of flow to the aortic pressure variations but do not indicate the magnitude of the change in resistance to flow under various circulatory conditions; hence the flow itself is underestimated.

AUTHORS.

Corrigendum

The title of the abstracted article by Benjamin A. Gouley on page 246 of the August issue of the Journal was incorrectly given. The corrected title and abstract are as follows:

Gouley, Benjamin A.: The Myocardial Degeneration Associated With Uremia in Advanced Hypertensive Disease and Chronic Glomerular Nephritis. Am. J. M. Sc. 200: 39, 1940.

A peculiar type of myocardial degeneration appears to be intimately associated with the uremic and preuremic states of arteriolar nephrosclerosis and chronic glomerular nephritis. It is found especially in those patients who have cardiac failure. The latter may be the outstanding feature of uremic intoxication. Pericarditis may be regarded as a complication of this myocardiopathy.

AUTHOR.

Book Reviews

RÖNTGENDIAGNOSTIK DES HERZENS UND DER GROSSEN GEFÄSSE: By Dr. Erich Zdansky, Vorstand der Röntgenabteilung am Krankenhaus Wieden in Wien. Wien, 1939, Julius Springer, 407 pages, 384 illustrations.

Roentgenologic examination of the heart and great vessels, and their relation to the lungs and mediastinum, is now a well-established procedure. It can be fully understood and appreciated only in conjunction with a sound knowledge of anatomy and pathology, and by correlation with clinical data in the broad sense of the word, i.e., by giving due consideration to constitutional factors, metabolic state, condition of the peripheral circulation, and to the functional status of the heart, as well as that of other organs.

Zdansky's book is an outstanding contribution. In addition to covering the subject very completely, it contains many fine original observations. The lucid presentation goes far beyond a description of roentgenograms; these are interwoven into a well-rounded, three-dimensional substance of clinical, physiologic, and pathologic observations. Thus the radiologist is revealed, not as a man solely absorbed with the technical interpretation of shadows, far removed from the bedside, but rather as a consulting physician.

It is a pleasure to state that a modern presentation of the subject of roentgenologic examination of the cardiovascular system is now available in three languages: Zdansky's book, in German; Laubry, Cottenot, Routier, and Heim de Balsac's *Radiologie Clinique du Coeur et des Gros Vaisseaux*, 1939, Masson et Cie., Paris, in French; and Roesler's *Clinical Roentgenology of the Cardiovascular System*, 1937, and *Atlas of Cardioroentgenology*, 1940, C. C. Thomas, Springfield, Ill., in English.

The quality of Zdansky's illustrations is of the high standard characteristic of Springer publications. Authors and editors in this country who may have been disappointed on seeing that the fine details of their original prints were lost in the process of reproduction—and this holds particularly true for roentgenograms and photomicrographs—ought to realize that the use of a screen with a fine grain is essential to faithful reproduction, in addition to good paper and careful, slow presswork. Insistence on this point will improve the quality of illustrations, although the cost is somewhat higher.

It is obviously impossible to do justice to Zdansky's book within the space available for a review. Only a few selected points will be considered.

Zdansky properly states that a carefully executed orthodiagram gives a more accurate estimate of absolute heart size than a teleroentgenogram, and he rightly warns against overrating the results obtained by kymography. The anatomic understanding of the roentgenograms presented in the three standard views is aided by beautifully colored schematic drawings. The importance of examining the heart in the right and left lateral recumbent positions, with a horizontal course of the roentgen rays, is stressed. A good explanation is offered for the plump appearance of the silhouette in infants and small children, with filling out of the waistline of the heart: the chest is deep and short, the angle of inclination of the heart—as seen in the lateral view—is relatively small, and the large vessels ascend less steeply than in older persons; therefore, in the anterior view, the silhouette appears to be foreshortened by projection, i.e., as if visualized somewhat from below. When speaking of measurement, the significance of the anteroposterior development of the heart is stressed, and it is pointed out that correlative measurements are of limited value because we are unable to express the development of the skeletal musculature

in mathematical terms, and the size of the heart is determined not only by its muscle mass, but also by the degree of filling, in which thickness and tonus of the heart muscle, heart rate, and venous return play a considerable role. Prolonged physical effort, including athletics, may lead to an increase in the size of the heart; this may be a physiologic process of adaptation, or a pathologic dilatation, and calls for clinical investigation.

With reference to heart disease, the author first discusses the radiologic features of enlargement of each of the four heart chambers, and stresses the functional aspects by referring to the inflow and outflow tracts of the two ventricles. The shapes of silhouettes and character of pulsations associated with the different types of valvular lesions are discussed. Reactivation of a rheumatic process in the heart is associated with hyperactive pulsations along the silhouette, and a rather acute increase in the size of heart may be observed; this, however, is reversible. Such an active endomyocarditis may well lead to heart failure, with no evidence of congestion of the lungs, as a rule. In cases of acute nephritis, with hypertension, the following interesting observations are made: Because of water retention, the diaphragm is abnormally high, and there is some pleural effusion on both sides; the cardiac shadow may be enlarged, often as a result of pericardial effusion; pulmonary edema of renal origin is present, and may escape clinical detection altogether, particularly when its location is chiefly central and interstitial. Zdansky has made interesting observations on the heart during the course of infectious and toxic conditions; he describes a latent dilatation which escapes detection when the size of the heart is studied with the patient standing up, but becomes apparent with the patient in the recumbent position: the dilatation is latent in the upright position because of inadequate filling of the heart as a result of peripheral vasomotor failure. There are good descriptions of the influence of anemia, metabolic disturbances, and vitamin B deficiency; also, ample space and illustrative material are devoted to cardiac aneurysm. For the radiologic diagnosis of chronic cor pulmonale, the value of the right anterior oblique view should perhaps have been stressed; in this view the prominence of the conus and the absence of left atrial enlargement are well demonstrated. Attention is directed to the inspiratory distention of the heart shadow which occurs in cases of emphysema and asthma, and also to changes in the silhouette caused by pleuropulmonary disease. Scoliosis with the convexity to the right causes a shift and rotation of the heart which give it a mitral configuration, whereas when the convexity is to the left there is an apparent widening of the aortic shadow. The funnel chest is responsible for a pseudoenlargement and mitral configuration of the cardiac silhouette. Intracardiac calcification is well illustrated.

Forty-four pages are devoted to a discussion of congenital malformations of the heart. The most interesting part is the explanation of that configuration designated as "coeur en sabot," which is associated with the tetralogy of Fallot. With this abnormality, the flow of blood in the right ventricle is diverted to the more right-sided aortic orifice, and hence an abnormal outflow tract is created, with its axis extending from the apical portion obliquely to the right, dorsad and craniad to the aortic orifice. Hence the waistline of the heart is not filled out, as would be the case with ordinary hypertrophy of the conus of the right ventricle, but is rather deepened, while the right ventricle projects to the left above the diaphragm and displaces the left ventricle dorsad. A case of tricuspid atresia shows what H. Taussig has described in this country. The different types of right-sided aortic arch are well covered, and the gourmand will enjoy the radiologic and anatomic description of the left-sided origin of the right subclavian artery.

In discussing pericardial effusion, Zdansky rightly points out the great difficulty of differentiating it from cardiac enlargement. With respect to the etiology of the effusion, some information may be obtained by observing the lung fields. An effusion of rheumatic or bacterial origin is not associated with pulmonary congestion. This may also hold true for the effusion of uremic origin, although the renal type of

pulmonary edema may be noted. In cases of effusion caused by cardiac failure, there will always be evidence of pulmonary congestion. In constrictive-adhesive pericardial disease, the cardiac shadow is either normal or moderately enlarged; marked enlargement is likely to be secondary to an associated valvular lesion, or to an encapsulated pericardial effusion. Irregularities in the contour may be characteristic, but mediastinal, interlobar, and diaphragmatic pleural thickening may give similar pictures. The amplitude of pulsations is much diminished, as a rule, although an increase, limited to the left side, is occasionally observed. He recommends testing for a change in the shape and position by studying the response of the mediastinal shadow to deep respiration, with the patient in the right and left lateral recumbent positions and with a horizontal course of the roentgen rays. Absence of a mediastinal shift in either position is indicative of mediastinal fixation, but this is also observed with other conditions, namely, bilateral pleural adhesions, a marked degree of cardiac enlargement, a large hydropericardium, pulmonary congestion, pleural effusions of considerable extent, and inability to take a deep breath. Calcification is the most conclusive evidence.

Special attention is devoted to the radiologic appearance of the lungs in cases of cardiovascular disease. An increase of pressure in the lesser circulation, such as may occur in connection with emphysema, kyphoscoliosis, pleural adhesions, or primary pulmonary sclerosis, is likely to exaggerate the arterial hilar shadows, and the pulsations of these vessels may be increased. The transparency of the lungs is not diminished. With pulmonary congestion the vascular structures become more marked, but their outline is less well defined, and the transparency of the lungs is diminished. Contributing to the characteristic appearance, there will be overfilling of the perivascular, peribronchial, and pleural lymphatics and hilar lymph-nodes, as well as transudation along the vascular and bronchial structures, or, in a circumscribed fashion, within the interstices and parenchyma. Small areas of atelectasis occur not infrequently. In the course of chronic pulmonary congestion caused chiefly by mitral lesions, multiple, small, dense nodules may be observed; they consist of true bone tissue. Chronic pulmonary congestion must be differentiated from chronic pulmonary edema. The latter occurs in connection with nephritis, essential hypertension, coronary artery sclerosis, aortic regurgitation, and mitral stenosis. It is not diagnosed clinically, as a rule, because of its central location and because it is exclusively or predominantly interstitial. It does not reveal a vascular pattern, such as is seen with the ordinary variety of pulmonary congestion, but is characterized by cloudy, inhomogeneous opacities, which, as a rule, leave free the apical and axillary portions of the lungs. Periarteritis nodosa may produce a similar picture.

Measurement of the aorta is made chiefly by the Kreuzfuchs method, i.e., in the anterior view the distance between the outermost point of the aortic knob and the left lateral contour of the barium-filled esophagus is ascertained. The width of the arch is thus measured. When there is elongation of the aorta, or a spread of the aortic loop caused by a high position of the diaphragm, the patient may have to be rotated slightly towards the right anterior oblique position. The average measurement for the healthy adult between the ages of 20 and 50 is 2.5 cm., with values as low as 1.8 cm., and as high as 2.8 cm. for the oversized person. Starting with the sixth decade, measurements of 2.7 to 3.0 cm. are still within normal limits. The amplitude of pulsations along the aortic shadow does not permit one to draw conclusions regarding the anatomic condition of the wall, for vascular tonus has much to do with these pulsations. Large pulsations occur when the vascular tonus is low, as in aortic regurgitation, active endocarditis and other infectious diseases, severe thyrotoxicosis, tabes dorsalis, Addison's diseases, and disturbances of blood pressure regulation; but in nephritic patients who have a high vascular tonus, the pulsations may be very small. Diffuse dilatation of the aorta may be caused by syphilis, as well as by atheromatosis. The former should be thought of when the patient is

middle aged and the heart is not enlarged. Calcification occurs with both syphilitic aortitis and atheromatosis. Diffuse elongation of the aorta, without appreciable dilatation, is caused by atheromatosis, without any elevation of blood pressure. An isolated dilatation of the ascending aorta is suggestive of syphilitic aortitis, but is not characteristic because it is also noted with arterial hypertension and aortic regurgitation and stenosis. Finally, the diagnosis and differential diagnosis of aortic aneurysm are discussed in detail.

Zdansky's book is an outstanding contribution and should be studied by anyone interested in the cardiovascular system who has a reading knowledge of German.

HUGO ROESLER

BAINTON AND BURSTEIN'S ILLUSTRATIVE ELECTROCARDIOGRAPHY: By Julius Burstein, M.D., Associate Electrocardiographer and Chief of the Cardiac Clinic, Morrisania City Hospital, New York, N. Y. Second edition, 1940, 277 pages, 106 plates, D. Appleton-Century Co., New York and London, $5.00.

The first edition of this book was regarded by one reviewer (AM. HEART J. 10: 566, 1935) as the best answer to the question, "What shall I read to learn something about electrocardiography?" In the opinion of the present reviewer, the second edition deserves a similarly hearty recommendation, in spite of the fact that the author ignores parasystole, the relatively common form of right bundle branch block described by Wilson, et al. (AM. HEART J. 9: 459, 1934), and the electrocardiographic changes which may be caused by pericardial effusion. His incorporation of numerous normal and abnormal precordial leads, together with the reports of the British and American committees which were appointed to recommend standard procedures for obtaining such leads, enhances the value of the book greatly.

Unfortunately, the English, especially the punctuation, leaves much to be desired. Perhaps such a barbarous neologism as "diphasism" will some day become respectable, but, at the moment, it produces in the reader the same uncomfortable feeling as does the expression "isoelectricity of the T wave."

The unconventional format lends itself well to the author's method of presenting his material, but it is the bane of librarians, and it makes the book hard to hold in one's lap.

HORACE M. KORNS

American Heart Association, Inc.

RADIO CITY

50 WEST 50TH STREET, NEW YORK, N. Y.

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

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**Executive Committee.*

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Original Communications

A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM IN UNGULATES, DOG, AND MAN

Part 1: The Sinoatrial Node

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Des Moines, Iowa

In 1907 Keith and Flack[1] described a neuromuscular node which they had found in the right atrial myocardium near the mouth of the superior vena cava. They stated that the structure of this tissue was similar to that of the auriculoventricular node, described by Tawara,[2] and that the heart beat originated in this node. Their statements were generally accepted, and used to supply the "missing link" in the chain of morphologic evidence in favor of the myogenic theory of the origin and transmission of the cardiac impulse. By ingenious electrocardiographic experiments, Lewis,[3] in 1913, showed that the heart beat originated in this region, and that the impulse spread thence to the rest of the heart. Thus, the node of Keith and Flack was established as the "primum movens et ultimum moriens" of the heart; and the node, together with the Purkinje system, became the morphologic basis upon which subsequent knowledge of conduction developed.

A study of the available literature on the sinoatrial node, however, brings to light many conflicting observations. Most experiments on ablation of the sinoatrial node fail to show convincingly that the node is the pacemaker of the heart (Flack,[4] Jaeger,[5] Magnus-Alsleben,[6] Moorhouse,[7] Brandenburg and Hoffmann,[8] Eyster and Meek,[9] and Borman[10]), and there is no unanimity of opinion as to the location, size, and structure of the node. The discoverers of the node say that it lies in the sulcus terminalis. In the human heart its muscle fibers are imbedded in dense fibrous tissue around an artery (or a circle of arteries) which is usually found on the caval side of the sulcus. This means that most of the node must lie on the caval side. According to Koch[11] the node is spindle-shaped, and the head of the spindle lies in the upper third of the sulcus, a millimeter or so below the angle made by the cava and

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the atrial wall. It tapers as it runs downward, and ends left of the middle of the inferior vena cava at its junction with the auricle. A slender fasciculus runs upward from the head, either over the cava or over the atrium. It is evident that Koch found the node on the atrial side of the sulcus. Walmsley[12] states that the node is spindle-shaped, and measures 20, by 3, by 1 mm. It gives off fine processes which pass over the superior vena cava and into the atrial musculature. In his illustration, the head of the spindle lies at the top of the sulcus. Bruni[13] modeled the node from serial sections of the hearts of cattle. His model of the node is composed of an upper "head," and a lower, "horseshoe-shaped" portion. The "head" lies across the upper part of the sulcus, and hornlike processes run from it, one on the cava, and the other toward the interatrial septum. The "horseshoe" portion straddles the superior vena cava at its entrance to the auricle. One end of the "horseshoe" runs anteriorly, and the other posteriorly, around the cava on the atrial side of the sulcus. In sheep, Bruni found only the "horseshoe" part. Blair and Davies[14] found only the "horseshoe" part in man and in cattle. Lewis[3] pictures the node, in the dog, on the caval side of the sulcus, head up. Shaner,[15] who also studied the node in cattle, found its anlage in the musculature of the superior vena cava above the sulcus, and states that it descends to the groove at birth. In the adult animal the node lies across the cava. Its upper part is separated from the atrium by connective tissue, but the lower portion is directly continuous with the atrial musculature. Mettam[16] found that, in the horse, the node is an ill-defined, whitish structure. Its long axis runs parallel to the sulcus, and it is 3 cm. long by 5 mm. broad.

Cohn,[17] Blair and Davies,[14] and others have found that the nodal tissue, in man, extends from epicardium to endocardium. In rabbits, Koch pictures it involving approximately half of the myocardium; the same is true in hogs, according to Lewis. Most of the investigators agree with the discoverers that the nodal muscle fibers form a network around, or lateral to, the artery (or arteries) in the sulcus. The tortuosity of the muscle fasciculi accounts, they assert, for the fact that such a network is not apparent histologically. Koch was not impressed by the network formation within the node. Blair and Davies state that most of the fibers run vertically, and that the sinoauricular node does not resemble the node of Tawara. According to most observers, the differentiating features of the special muscle elements are the following:

1. The fibers are a trifle more slender than ordinary atrial fibers.

2. The fibers are faintly striated (Yater,[18] Burian,[19] Blair and Davies,[14] and others). Burian, and Blair and Davies also described a clear perinuclear zone comparable to that found in Purkinje fibers.

3. The nodal fibers are tortuous.

4. Branching is frequent.

5. The nuclei are round or oval, and, occasionally, multiple.

6. The nodal elements are directly continuous with the atrial and the caval musculature.

7. Keith and Flack found ganglion cells and nerve trunks within the substance of the node. Subsequent observers, however, located these around the periphery of the node.

8. Several observers have noted that the muscle fibers of the node are directly continuous with the musculature of the nodal artery.

In order to "illumine that which to us was dark," we undertook a gross and microscopic examination of the sulcus region in thirteen human, six canine, eight bovine, seven ovine, three porcine, and two equine hearts. The hearts used for gross dissection were fixed in Kaiserling I. The blocks used for microscopic study were fixed in Bouin's solution, or in a 10 per cent solution of formalin. The sections were stained routinely with iron hematoxylin, and at times counterstained by van Gieson's method. Sections were cut longitudinally at three levels, viz., the atrial side, the bottom, and the caval side of the sulcus terminalis, and, transversely, from the upper, middle, and lower parts of the sulcus. For comparative purposes, the regions around the pulmonary veins, the inferior vena cava, and the pulmonary artery, as well as various places in the right and the left atrioventricular groove, were studied grossly and microscopically.

GROSS ANATOMY OF THE NODAL REGION

This part of our investigation was undertaken because Walmsley states that the node can be exposed by gross dissection, and can be seen, when the epicardium is removed, as a yellowish body lying deep in the upper part of the sulcus. When we carefully removed the pericardium and the loose areolar tissue from the atrium and the veins, the arrangement of the regional muscles was revealed. The most striking feature which was observed during the removal of the epicardium was the large number of nerve trunks running over the great veins and over every part of the atria. A second outstanding feature was the extension of the atrial musculature from one-fourth of an inch to 2 inches up the walls of the great veins.

Perhaps the muscular arrangement in the region of the superior vena cava can be best described by beginning with Bachman's bundle.* This is a stout band of muscle which extends transversely behind the aorta, between the anterior portions of the bases of the auricular appendages. At the right end of this bundle the fibers spread out fanlike, forming a continuous sheet which extends over the right atrium posteriorly to the left of the vena cava, around the cava itself, over the edges and the bottom of the sulcus terminalis, and over the right auricular appendage. Thus, the cava lies in the buttonhole-like opening of this sheet. When

*Fasciculus interauricularis horizontalis (Tandler, J.: Anatomie des Herzens, Jena G. Fischer, 1913).

the fibers enter the sulcus, they become surrounded by loose connective tissue in the bottom of the sulcus, continue downward the length of the groove, and extend below it, near the endocardium, toward the atrioventricular groove. In the hog, and in other animals, also, these fibers form a distinct bundle which runs to the auriculoventricular groove on the acute margin of the heart. This band is, perhaps, the bundle which French writers have described as the direct connection between

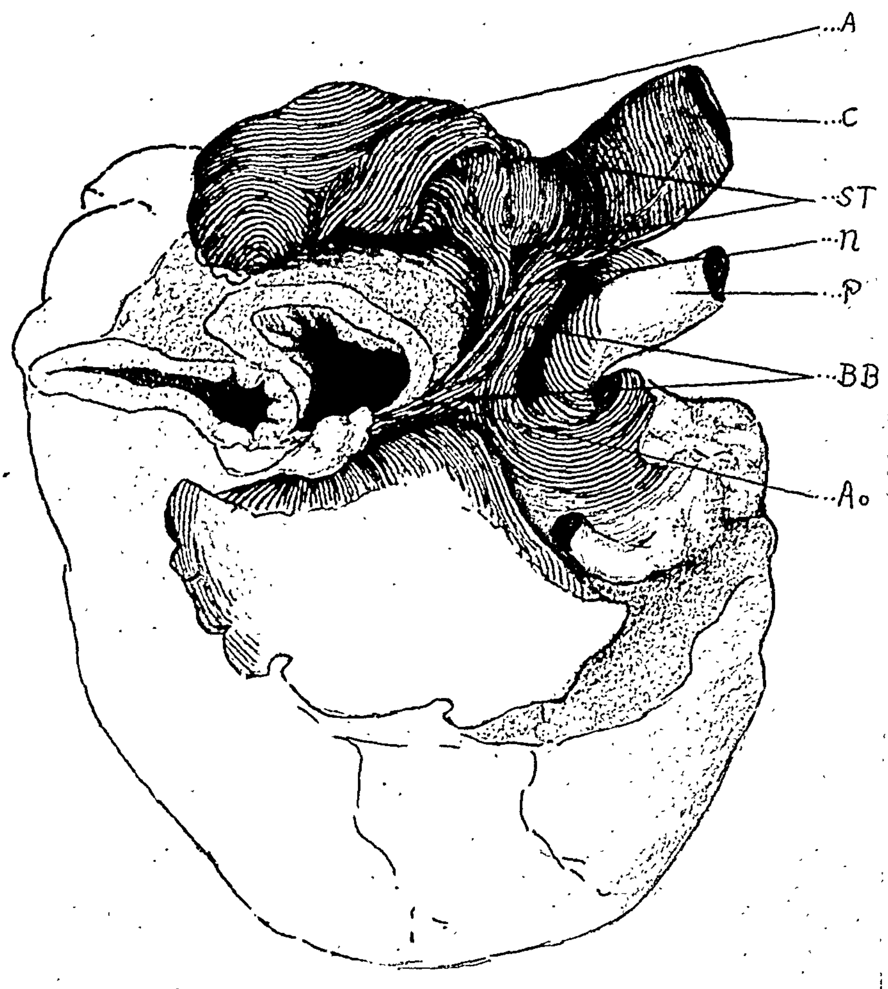

Fig. 1.—Region of the sulcus terminalis from above and behind, showing muscular arrangement of the human heart. The epicardium has been removed and the vena cava bent forward. *A*, Auricular appendage. *C*, Vena cava. *ST*, Sulcus terminalis. *N*, Nerve going up over cava. *P*, Pulmonary vein. *BB*, Bachman's bundle. *Ao*, Aorta.

the sinoauricular node and the ventricle. The fibers directly to the left and in front of those which lie in the bottom of the sulcus form the outer, left edge of the sulcus terminalis. These fibers extend downward like a sleeve, and, in the lower part of the sulcus, turn to the right. The upper fibers of the sleeve run over the cava, forming Wenckebach's bundle, and the lower ones continue backward to the left atrium. The surface of the sleeve has a mattressed appearance because of the fact that numerous connective tissue trabeculae separate the fasciculi. As the fibers of the sleeve turn to the right, over the cava, they become

the "nodal" fibers of this locality, and are separated by loose connective tissue from those, already described, which run toward the auriculoventricular groove. Thus, the nodal tissue is but a segment of the myocardium.

The arrangement of the muscle fibers in the sulcus region was practically the same in all of the species studied, although the amount of connective tissue varied. The larger the animal, the more conspicuous and widespread was the supporting tissue. It was firm and easily seen in the horse's heart, but was scarcely perceptible to the naked eye in the heart of the small dog and lamb. In the human heart it forms a tough shred which surrounds the "nodal" artery.

The architecture of the myocardium around the pulmonary veins is not essentially different from that around the superior vena cava, and, when a pulmonary vein enters the atrium obliquely, as does the cava, a sulcus is formed, and the muscle fibers therein are of the same type and are surrounded by the same kind of connective tissue as that in the sulcus terminalis.

We found that the histologic structure of the nodal region is substantially as it has been described by other investigators. The network which is so characteristic of the node of Tawara was not present in the node of Keith and Flack in the hearts that we examined. In the upper part of the sulcus the fibers run nearly parallel to the crista terminalis and are arranged in small bundles which are separated by an abundance of connective tissue (Fig. 3*B*). In cross sections through the upper part of the sulcus the fibers are cut transversely. Here the "nodal" structure occupies the entire thickness of the myocardium. It is triangular, with its base resting on the endocardium. As the amount of connective tissue lessens, toward the sides of the triangle, the peculiarities of the muscle fibers disappear. Farther down the sulcus, where the sleevelike band of muscle turns to run across the cava, the fibers are cut obliquely or longitudinally. However, these are not the fibers which are encountered in the upper portion of the sulcus. At this level those fibers have lost the great amount of connective tissue which surrounded them, and now appear as ordinary muscle elements, next to the endocardium. The fibers that are cut longitudinally lie under the epicardium, run to the right, over the cava, and, for the most part, merge with the caval musculature (Fig. 2). A few of them, however, end in the thick walls of the vessels which lie in this region. To the left, on the other hand, the fibers continue as ordinary myocardial elements.

In the sheep and dog heart, in which the connective tissue is scant, and in the human heart, in which there is much loose connective tissue, both at the upper edge of the muscle sleeve running across the cava and in the space between it and the endocardial myocardium, many of the muscle fibers are slender and tortuous (Fig. 2). Such fine, wavy fibers also run parallel to the posterior wall of the cava in the human, canine, and ovine heart.

The number of the "peculiar" fibers in the sulcus varies with the amount of connective tissue which surrounds the caval entrance. There are very few in the dog and sheep, but many in the horse and ox. Branching of the muscle fibers of the caval region is not more frequent than in other parts of the myocardium. The striations of the fibers in this region are always indistinct, but can be seen in sections which have been properly fixed and stained (Fig. 2*B*). We have not noted any special, clear, perinuclear space, such as was described by Burian. The nuclei are round when the fibers are cut transversely, oval when they are cut obliquely, and rod-shaped when they are sectioned longitudinally, except in the case of fibers that have a diameter of four microns, or less. In such cells the nucleus is spindle-shaped. Multiple nuclei are no more frequent than in ordinary myocardial elements.

The fibers of the nodal region, therefore, differ from neighboring muscle elements in that they are slightly smaller in diameter, less distinctly striated, and more tortuous. Naturally, one raises this question: Do such differences justify calling this a region of specialized muscle? If they do, ordinary muscle elements should not possess these characteristics. In order to learn whether or not such is the case, we examined, microscopically, the heart wall at the junction of the atrium with the inferior vena cava, the coronary sinus, and the pulmonary veins, and at the junction of the pulmonary artery with the ventricle, as well as at various places in the right and left atrioventricular groove. Our observations follow:

1. Tortuous, slender muscle fibers were present in all of these places, and, indeed, in other parts of the atrial and ventricular walls. Such fibers occur frequently as bridges between the atria and the ventricles in the auriculoventricular groove of young human hearts, and also in the hearts of the other species.
2. We were, therefore, able to verify the statement, made by Kent,[20] that there are, in man and other mammals, definite muscular bridges between auricles and ventricles at various places in the auriculoventricular groove.
3. Oval and round nuclei are present in the slender muscle fibers wherever they occur.
4. The indistinct striations which are characteristic of the muscle fibers in the sulcus terminalis also occur in the muscle fibers that are surrounded by excessive amounts of connective tissue elsewhere in the heart.

The large, open vessel shown in Fig. 2, which is located either in the center or to the side of the Keith and Flack node, has usually been described as an artery. We have never found an internal elastic membrane nor the intima characteristic of an artery in this vessel. Hence, we believe that the vessel is a thick-walled vein. Many such veins were found around the cava in the hearts which we studied. Arteries were

also present, but they were much smaller, and had the structure typical of such vessels.

The most surprising feature encountered in our histologic investigation was the abundance of nerve tissue in both atria and in the auriculoventricular groove. Nerve cells and collections of nerve fibers were most numerous in bovine hearts. Ganglion cells and nerve trunks were prevalent in the epicardium of the sulcus terminalis. Collections of ganglion cells surrounded the caval ostium. Fig. 2 shows a small group of nerve cells and a large nerve trunk (human heart). Fig. 3*A*

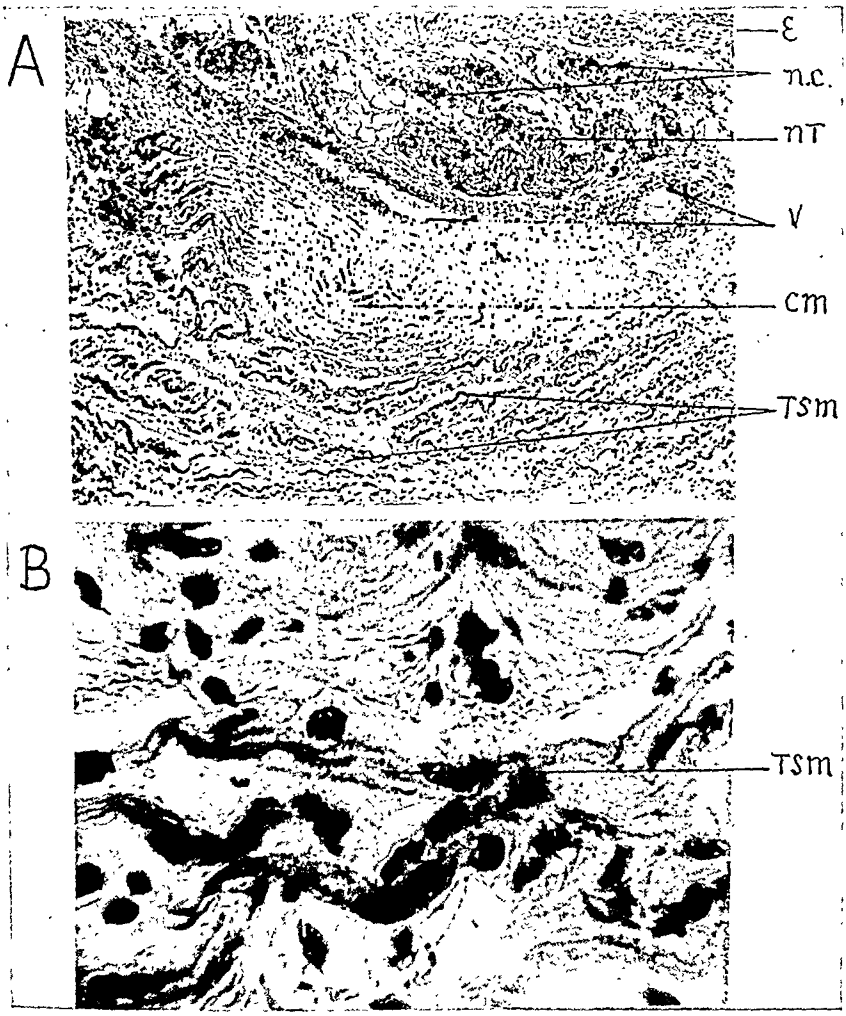

Fig. 2.—Cross section from lower half of the sulcus terminalis (human heart) (×75). In *A*: *E*, Epicardium. *NC*, Nerve cells. *NT*, Nerve trunk. *V*, Vein. *CM*, Caval muscle. *TSM*, Tortuous, slender, muscle fibers. In *B*: *TSM*, Tortuous, slender, muscle fibers, showing striations (×760).

shows a group of ganglion cells behind the cava (bovine heart). The aggregations of nerve cells consist of either small or large cells; the latter predominate. Near the entrance of the inferior cava, and to the left of it, there were huge groups of nerve cells. Scattered nerve bundles and nerve cells were found in the epicardium of the entire left atrium. Nerve fibers were also observed in the walls of all of

the pulmonary veins which were examined, and small groups of ganglion cells were found in the atrial wall near them.

In our search for muscular bridges in the auriculoventricular groove, nerve fibers and ganglion cells were found in practically all of the localities which we examined, in all of the hearts. Furthermore, as will be shown in Part II, nerve fibers and nerve cells are abundant at the top of the interventricular septum. These form a wreath of nerve tissue which surrounds the entire heart at the junction of its upper and lower chambers.

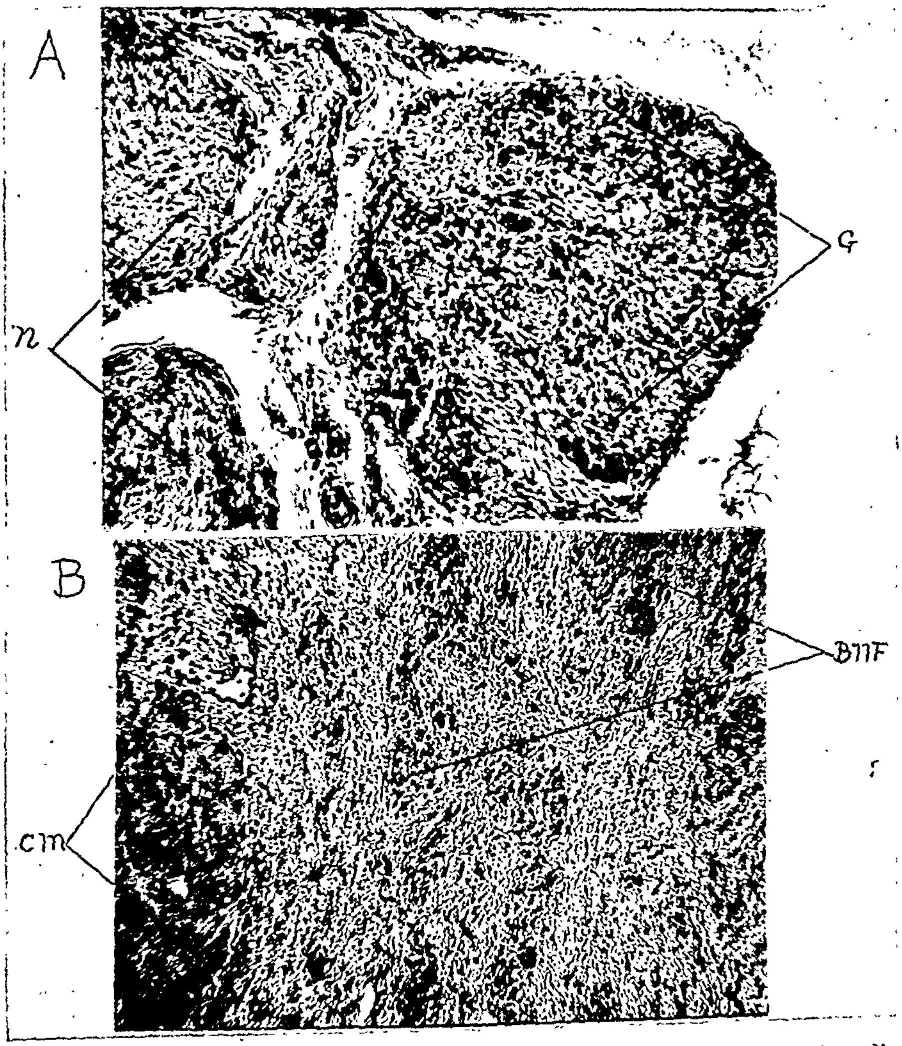

Fig. 3.—Region of the sulcus terminalis. In *A:* Bovine heart. *G*, Ganglia. *N*, Nerves. In *B:* Equine heart. Upper part of sulcus. *BNF*, Bundle of nodal fibers in dense fibrous tissue, cut transversely. *CM*, Caval muscle.

COMMENTS

It seems to us that our observations clarify many of the puzzling statements in the literature on the anatomy and physiology of the sinoatrial node. Dissection of this region discloses a stout, transverse band of muscle which runs between the bases of the right and left auricular appendages. From the right end of this band, a sheet of muscle spreads out fanlike to envelop the superior vena cava posteriorly

and anteriorly, to form the bottom and the sides of the sulcus terminalis, and to form a part of the wall of the right appendage. The part of this sheet which happens to lie in the bottom of the sulcus and its immediate neighborhood is what has been described as the node of Keith and Flack. The fact that the muscle fibers in this region become a little more slender and are less distinctly striated is to be ascribed, we think, to their environment. Hence, "nodal" muscle fibers exist on both sides of the caval entrance, as well as below and above it. This muscular arrangement accounts for the lack of agreement concerning the shape and location of the node. It also explains why those who were familiar with the histologic appearance of the fibers in this locality could always find "nodal" fibers remaining in the uninjured atrium, even after extensive destruction of the region, for the point where a given "nodal" fiber ceased to be "special" and became ordinary myocardium was purely a matter of judgment.

This study does not shed any direct light on whether the slight change which takes place in the size and structure of the fibers in the sulcus region is of such a nature as to make them the "primum movens et ultimum moriens of the heart," but it does, we believe, invalidate the general conclusions that the results of experiments on the node are exclusively myogenic. Until we exclude the possibility that the thousands of nerve fibers and ganglion cells in the walls of both auricles may affect the results, it cannot be held that the physiologic and electrical phenomena which are observed in such experiments are caused solely by muscular activity. Furthermore, these nerve elements in the atrial walls must be taken into account in any study of atrioventricular conduction, both in health and in disease.

CONCLUSIONS

1. A morphologic study of the region of the sinoatrial node in the human, equine, porcine, bovine, and ovine heart discloses the fact that the node of Keith and Flack is only a segment of a sheet of muscle which covers the first part of the vena cava superior, and spreads to the left to form the atrial myocardium.

2. The fibers of the sheet which lie in the bottom and on the sides of the sulcus terminalis become more slender and show less distinct striations when they are imbedded in connective tissue. These alterations disappear when the supporting tissue is of the same amount and type as that found in the surrounding myocardium.

3. Nerve trunks and groups of ganglion cells were found in the epicardium where the superior vena cava enters the heart, and around other veins of both atria, in all of the hearts which were studied.

4. Muscle fibers which were identical in size and structure with those in the sulcus terminalis were found in many places in both the atrial and the ventricular walls.

5. A wreath of ganglion cells and nerve fibers surrounds the heart in the atrioventricular groove.

6. Many muscular bridges between the auricle and ventricles were found in the auriculoventricular groove.

7. It is suggested that the nerve elements which are scattered profusely over the atria and in the auriculoventricular groove must be taken into account before a proper understanding of cardiac conduction, both in health and disease, can be attained.

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THE MECHANISM AND NATURE OF VENTRICULAR FIBRILLATION*

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VENTRICULAR fibrillation, first described by Ludwig and Hoffa,[1] in 1849, and called *mouvement fibrillaire* by Vulpian,[1] in 1874, is an incoordinate type of contraction which, despite a high metabolic rate of the myocardium,[2] produces no useful beats. As a result, the arterial pressure falls abruptly to very low levels, and death results within six to eight minutes from anemia of the brain and spinal cord. Abrupt apnea, followed by asphyxial gasps, pallor, cessation of all pulsations and heart sounds, and loss of all reflexes are the clinical earmarks of death from ventricular fibrillation.

Not all animals are equally susceptible, and the degree of ventricular incoordination is not equally marked. In the frog and turtle, fibrillation is induced with difficulty, and is of a coarse, undulatory type. It is generally accepted that the hearts of fowls and small mammals (mouse, rat, cat, rabbit, hedgehog, monkey) are more likely to recover spontaneously, but there are marked variations in different animals of the same species.[1] In the hearts of larger animals (dog, sheep, goat) the condition is irrevocable. We have records of over 400 cases of fibrillation in dogs, and have witnessed only a single recovery. We believe that recovery is certainly rare in man when the ventricles are entirely normal.

In mammalian hearts, it has been observed as a result of (a) experimental occlusion of a coronary vessel, (b) stimulation with prolonged, direct, alternating or faradic currents, or with brief single shocks applied late in systole, (c) the use of toxic doses of many drugs, and (d), occasionally, as a result of mechanical, chemical, or thermal irritants. So-called "spontaneous fibrillation" is probably assignable to one of these unrecognized factors.

In man, it is often a terminal event in various forms of cardiac failure; indeed, most of the published electrocardiograms were taken from moribund patients. It is apparently the cause of sudden death following the inhalation of chloroform, benzol, cyclopropane, and other vapors. It may prove to be, more often than we think, the cause of sudden death after (a) severe blows upon, or other trauma of, the chest, with or without obvious injury to the heart, and (b) in cases of stab, arrow, or bullet wounds in which death is not the result of hemorrhage and cardiac tamponade. However, *the most common causes* of human

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ventricular fibrillation are (c) sudden occlusion of coronary vessels (usually thrombosis), and (d) electrocution, accidental or purposeful.

My own interest in ventricular fibrillation was awakened by the need of conserving laboratory animals during experimental work, for both humane and economic reasons. Although materialistic motives were an incentive to understand ventricular fibrillation and to seek means for its prevention and arrest, the hope has survived that, eventually, facts so gathered might have some practical human application.

In cardiodynamic investigations which were begun in 1912, it was necessary to stab a ventricle with the cannula of an optical manometer, or with an instrument for producing valvular lesions. In such experiments one becomes impressed with the great resistance of the heart to injury or severe manipulation. Occasionally, however—far too often, indeed—a quick stab, a slight adjustment of a trocar, or an apparently trifling insult resulted in unexpected fibrillation. It occurred in the hearts of young and old dogs alike, in hearts in good, as well as poor, dynamic and nutritive states. It gradually became evident that I was repeating experiments reported by Kronecker and Schmey,[1] in 1884, with the difference that fibrillation occurred without regard to what areas were punctured. Between 1912 and 1920, various measures were tried to avoid such disasters in experimental work, e.g., changing anesthetics or using a combination of anesthetics, cooling dogs to 30° to 32° C. before experiments were started, stimulating cardiac nerves, and employing drugs such as digitalis, quinidine, adenylic acid, etc., as prophylactics, but all were without obvious benefit.

A clue to the cause of fibrillation produced in this way began to appear in 1925,[3] during an investigation of the reactions of the ventricles to surface stimuli. May I point out that it was then demonstrated that the mammalian ventricle is not refractory to stimuli throughout systole, as is generally believed, but that it reacts during the last 0.06 second of systole by a contraction in early diastole. It is interesting to note, parenthetically, that not until 1940 were the ventricles of the frog and turtle shown to be similarly nonrefractory (Shannon and Wiggers[4]).

In our zeal to ascertain the earliest moments of responsiveness of the dog's ventricle, very strong induction shocks were sometimes used. It was found, to my disappointment—as far as studies then in progress were concerned—that fibrillation was often induced by such a single induction shock. Taken in conjunction with similar experiments of Mines[5] and de Boer[6] on the frog's heart, they seemed to indicate that late systole constitutes a period during which the ventricle is especially vulnerable to stimuli, and that the incidence of fibrillation from punctures is not a topographic, but a temporal, matter. However, the clue did not then reach a "publication threshold." Subsequently, Andrus, Carter, and Wheeler[7] induced atrial fibrillation by a single induction

shock; and Ferris, King, Spence, and Williams[8] produced ventricular fibrillation in rams by applying direct current shocks, 0.03 sec. in duration, to the chest wall during the inscription of the T wave of the electrocardiogram. This they interpreted as the partially refractory period. More recently, Wegria and I[9] demonstrated unequivocally that the application of very short condenser shocks locally to a spot on the ventricle induces fibrillation when the shocks fall during late systole, but never at any other phase of the heart cycle. We therefore designated this the *vulnerable phase* of systole. The results have now been confirmed, under various nonvolatile anesthetics, on cats and dogs, as well as on decerebrated cats. Ventricular fibrillation occurs under a wide range of dynamic conditions, including hypertension, shock, and myocardial failure, as well as during anoxia, asphyxia, and hypercapnia. How these many influences modify the threshold remains to be determined. It is induced by stimulating any spot on the ventricular surface; specific fibrillation areas do not exist. A brief rectilinear shock (ca. 0.01 to 0.03 sec.) and a single or partial sine wave are similarly effective, but only when they fall during the vulnerable period.[10, 11] More prolonged direct current or alternate current shocks induce fibrillation only when an effective moment of the stimulus falls during the vulnerable period of a normal or a premature systole.[10, 11] Spread of current is not a factor in the induction of fibrillation.[12]

Certain fundamental facts emerge from studies so far completed: (1) Fibrillation is started by a highly localized stimulus which must, however, reach a certain strength; otherwise, only a premature beat results. (2) It is not necessary to pass a current through the rest of the myocardium in order to induce fibrillation. (3) The capacity to fibrillate is inherent in heart muscle; it does not require the sensitizing action of nerves or the presence of epinephrine or related substances, although admittedly these may be found to affect the fibrillation threshold. Miss Maltby and I found, in 1929 (unpublished work), that fibrillation is easily induced in the cat's ventricle after perfusion for many hours with Locke's solution, which certainly must have washed away all traces of body hormones.

THE EVOLUTION OF VENTRICULAR FIBRILLATION

Cinematographic studies[13] strongly suggest that ventricular fibrillation cannot be adequately described as an asynchronous contraction of ultimate myocardial fractions (fibers?). The incoordination and asynchronism first involve comparatively large sections of the myocardium, which progressively multiply and decrease in size as fibrillation continues; but, even in the stage of fine fibrillation, asynchronism in the contraction of adjacent fibers does not seem to occur. The contractions are initially vigorous, but fail to elevate ventricular pressure because conduction is slow, summation of fractionate contractions is thereby

delayed, and different blocks do not contract synchronously. As myocardial anoxia develops (because of interruption of coronary flow), the vigor of contractions decreases until, within thirty to forty-five minutes, all visible signs of movement cease.

That there are four general stages, as previously described,[13] has been amply confirmed by our recent studies; but greater thought and experience suggest certain reinterpretations and amendments.

The first, or undulatory, stage, previously called the tachysystolic stage, is very short; it lasts for only a second or two. However, its analysis is highly important for the light it sheds on the mechanism which starts the fibrillation. Careful, direct observation or slow-motion pictures show that the ventricle undergoes three to six undulatory contractions which have many of the earmarks of premature systoles. The contraction wave spreads more slowly than normal, and in several directions from the area stimulated. This is represented schematically in Fig. 2*A,* in which the two dots indicate the stimulated points. A fair degree of coordination exists, in the sense that fairly large areas are excited in sequence. These contractions are slightly preceded by aberrant ventricular complexes in electrocardiograms recorded by standard leads. Consequently, I previously concluded, with other observers, that fibrillation is initiated by a short run of premature contractions, and called this the tachysystolic stage. More careful study of a large number of instances of fibrillation, particularly those induced by single shocks, favors the interpretation that only the first of these beats represents a true premature contraction, elicited by the focal stimulation. The remainder are apparently caused by re-entrant waves. In the first place, a careful re-examination of the motion pictures indicates that the surface waves of contraction do not follow quite the same path or areas. The evidence for this cannot be presented in print. Secondly, the periods of the sequential electrical deflections in the standard leads become progressively shorter, and the configuration of successive deflections changes progressively. This is illustrated by Fig. 1. In curve *A* the introduction of one sine wave (*St*) during the vulnerable period caused a single premature contraction; the complete course of the aberrant deflection is indicated by *QRT,* with a superimposed *P.* This resulted in a barely recognizable rise of intraventricular pressure (wave *E.*) When a different phase of the same shock (*St*) strikes the vulnerable period, as in curve *B,* it produces an almost identical premature electrographic deflection (QRT) and a slight rise of pressure (*E*), but this is followed by four electrical deflections of diminishing periods and different configurations. These deflections, which represent the introductory undulatory phase, change abruptly at *X,* where the convulsive stage develops. Occasionally, this undulatory stage is more prolonged, as shown in Fig. 1, Curve *C,* in which case the undulatory and convulsive stages are not so clearly demarcated. The effect of these aberrant

excitations on ventricular pressures is very variable. Sometimes only the first premature beat causes a small pressure elevation, but it may be much more definite than any shown in records illustrating this article. Occasionally, there are no changes except those which result from atrial contractions, as shown in Fig. 1*C*. Again, the second, third, or fourth beat may cause a larger rise of pressure than the first, as illustrated in Fig. 1*B*. Such effects are never observed as a result of repeated electrical stimulations during diastole, which evoke true premature beats.

The second stage, that of *convulsive incoordination*, lasts from fifteen to forty seconds. It is characterized by more frequent waves of contraction, which sweep over smaller sections of the ventricles. Each area still executes fairly powerful contractions; but, inasmuch as not all masses contract in phase, the ventricle is pulled about in a convulsive manner. The term "flutter" does not describe the appearance of these movements very well, and hence is avoided.

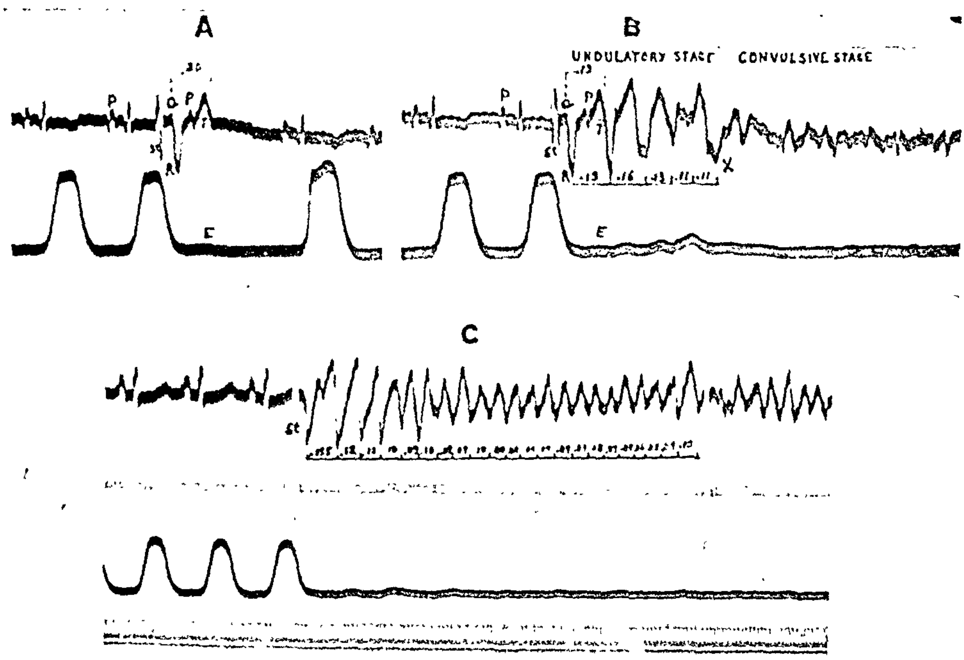

Fig. 1.—Curve *A*, Electrocardiogram (Lead II) and left ventricular pressure curves, illustrating the production of a premature beat QRT by a single sine wave (*St*), and the delayed effect on left ventricular pressure, *E*. Curve *B*, Similar records from the same experiment, showing effect of a single sine wave (*St*) during the vulnerable period of systole. Note the same initial QRT, followed by deflections of changing configuration and reduced periods. Curve *C*, Similar records from another animal showing same features except a prolongation of the undulatory stage.

The third stage, that of *tremulous incoordination (Herzzittern)*, lasts two to three minutes. The surface of the ventricles appears to be broken up progressively into smaller and smaller independently contracting areas. These multitudinous contractions of fiber groups, all out of phase, give the heart its tremulous appearance, and generally cause an increase in the frequency of electrocardiographic waves.

In summarizing these stages, one may say that ventricular fibrillation is never an asynchronous, incoordinate contraction of individual fibers, as the name implies. Rather, the incoordination and asynchronism involve smaller and smaller areas or masses of myocardium, until, in the tremulous stage, there are innumerable groups of contracting fibers.

The fourth stage, that of *atonic fibrillation,* develops when the increasing anoxia causes depression of contractile force, slows conduction, and, eventually, leads to regional blocks and complete failure of contractility. It usually develops within two to five minutes after the onset of fibrillation, and is characterized by the slow passage of feeble contraction wavelets a short distance over the ventricular surface. Progressively, more and more areas become quiescent, and, in the end, the region overlying the interventricular septum alone shows a lazy passage of waves.

THEORIES AS TO THE NATURE AND MECHANISM OF VENTRICULAR FIBRILLATION

As to the fundamental mechanism of fibrillation we have plenty of theories, but none is universally accepted. Space is lacking to review the different hypotheses, but we may note in passing that they all center around two ideas, viz., (a) that the impulses arise from centers, or pacemakers, or (b) that the condition is caused by the re-entry of impulses and the formation of circles of excitation. Each of these views, again, has two groups of exponents, viz., (a) those who believe that a single focus, or excitation ring, occurs, and (b) those who favor the idea that multiple foci, or numerous circus rings, are developed. Obviously, all of these conceptions revolve about the mechanisms which are in operation when fibrillation has been fully established; they do not deal with the processes which initiate fibrillation, or with those which explain its evolution. Although we are not yet in a position to suggest any hypotheses which satisfactorily explain either the inception or the evolution of the fibrillation process, we may profitably examine the clues which recent experimental work offers.

THE INITIATION OF FIBRILLATION

A satisfactory theory as to the onset of ventricular fibrillation must explain (a) the re-entry of impulses which causes the primary undulatory beats, and (b) the generalized disorganization of ventricular conduction by a strong, momentary stimulus which is essentially limited to one locality on the ventricular surface. It must further account for the facts (c) that a brief stimulus, or the effective portion of a prolonged one, must fall exactly in the vulnerable phase of late systole, and (d) that, if the strength of such a stimulus is inadequate, only a premature contraction results, i.e., that the conditions for re-entry and induction of undulatory beats are not created. We may profitably examine to what extent these coefficients can be explained by recent

experimental work, and state with greater exactness the problems that remained unsolved.

The demonstration that brief shocks, when applied locally to the ventricle, can cause a response, i.e., either a premature contraction alone, or such a contraction followed by undulatory beats and true fibrillation, indicates clearly that some fractions of the myocardium have passed out of their refractory state before the end of systole, which is demarcated by the incisura of ventricular or aortic pressure curves, or by the end of the T wave in the electrocardiogram. Such a probability has been previously analyzed by the author in a theory of the summation of fractionate contractions.[14] Such an asynchronous offset of fractionate contractions, caused either by the slight delay in their onset or by variations in their durations, is, as King[15] has properly emphasized, essential to any concept of the initiation of fibrillation. Unfortunately, such an analysis does not go far enough; it fails to explain why a strong, brief stimulus, when applied during the vulnerable period, induces fibrillation, whereas a similar, but weaker, shock is followed only by a single premature beat. Frankly, this question cannot now be answered, but certain facts allow us to extend the analysis into channels that may lead to new experimental ideas.

It is possible that the premature beats which are elicited by diastolic stimuli and by those applied during the vulnerable period are not initiated in exactly the same way. It is conceivable, for example, that the impulse which is initiated by diastolic stimuli at once spreads radially from a discrete focus; whereas an impulse which is started during the vulnerable period may find many adjacent fractions still refractory, and therefore weave its way to form a broader wave front during the first 0.02 to 0.03 second, i.e., until all muscle fractions have become nonrefractory. Thus, as is illustrated crudely in Fig. 2*B*, the sinuous passage of impulses from x to y may cause the formation of a wave front at y, from which the sweep of excitation responsible for the premature beat proceeds. In any event, the longer intervals between stimuli and mechanical responses and between the onset of electrical and pressure deflections in the case of premature systoles which are elicited during the vulnerable period (cf. Fig. 1*B* and *C*) suggest that there is some sort of delay in their initial spread.

The fact that only strong stimuli, applied during the vulnerable phase, are followed by undulatory waves and fibrillation can be interpreted to signify that they exert some influence at a distance, which modifies conduction and permits re-entry, or that more muscle fractions are excited under the active electrode, thereby forming a different type of wave front, from which conduction proceeds over the myocardium. Inasmuch as we are limited to analyzing only contraction and electrical phenomena on the surface of the ventricles, it is extremely difficult to obtain evidence in favor of either hypothesis. However, a priori, the

idea that a strong, brief stimulus creates a local condition responsible for re-entry of waves seems the more plausible. Even speculations as to *how* the local action of stronger currents can produce the conditions necessary for re-entry of impulses, e.g., longer pathways, slower conduction, or shorter refractory states in muscle fractions, are still difficult to formulate. We have suspected that, by stimulation of more reactive fractions, a broader wave front may be formed at *y* after stronger stimuli, and that, in this way, the wave of excitation spreads slowly over aberrant channels, perhaps muscle bundles, to the opposite ventricle, whereas with weaker stimuli the opposite ventricle is apparently excited *via* its bundle branch.[3] A forward step would be taken if it could be demonstrated that fibrillation occurs only when the impulse which is released also causes a premature summation beat of the opposite ventricle, instead of a delayed, but normal, type of contraction, such as occurs after diastolic stimuli.[3] The existence of slowed conduction and longer pathways, the two prime factors in re-entry, would thus be established.

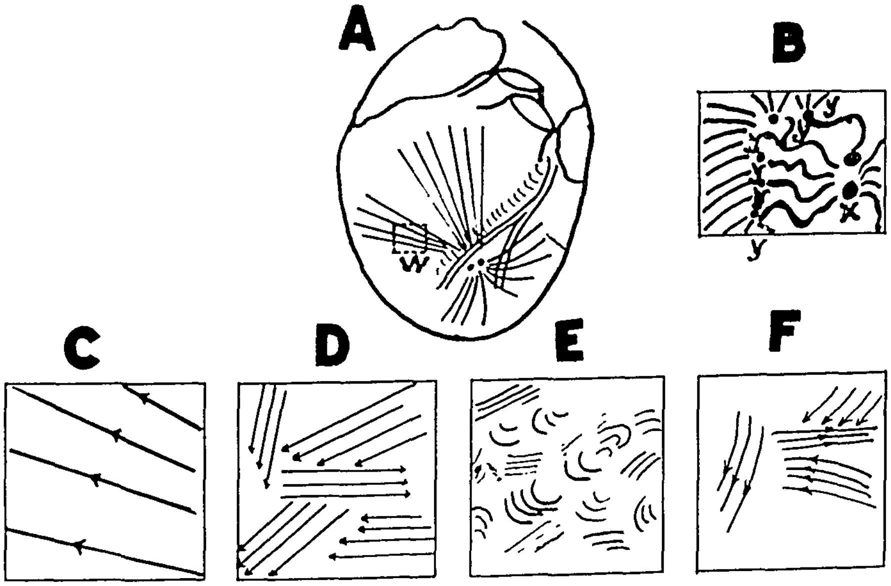

Fig. 2.—Diagrams indicating the spread of waves, observed in analysis of moving pictures, during stages of fibrillation. *A*, spread of wave front during initial, undulatory stage. *B*, Theoretical passage of impulses from point *x* to form a wave front at *y*. *C-F*, Appearance of contraction waves in small rectangular area *W*, magnified: *C*, undulatory stage; *D*, convulsive stage; *E*, tremulous stage; *F*, atonic stage.

MECHANISMS OF EVOLUTION

It may be stated at once that, in my opinion, the known experimental facts are best explained by the theory that a re-entry of impulses and formation of limited circuits occur throughout the evolution of fibrillation. However, it is necessary to amend this general statement in two respects: 1. As the fibrillation advances, the distances traveled decrease, and the number of muscle masses which are excited independently increases and becomes smaller. 2. Inasmuch as sequential excitations travel over a bulky mass of ventricular muscle, we must not

think in terms of two-dimensional rings or circuits, but rather of massive *impulse fronts* spreading in three dimensions.

During the undulatory stage we can conceive of several (probably never one) long circuits of impulse fronts which excite muscle fractions in an orderly manner, but in slow sequence. In this way, a slow recruitment of fractionate contractions occurs in several sections of the myocardium; indeed, it is not impossible that they follow muscle bundles. However, inasmuch as the summations of recruited fractionate contractions are not synchronous in different sections, the beats of the ventricles as a whole at once become ineffective, elevating intraventricular pressure only a trifle, if at all.

With the onset of the *convulsive stage* the circuits of impulse fronts abruptly become smaller, perhaps because they interfere with each other and are annihilated as wave fronts collide, and because there is some decrease in rate of conduction as a result of progressive increase in anoxia.

If, during the progressive development of fibrillation, as described above, the behavior of any definite surface region—say 2 to 4 cm. in diameter—is analyzed in the motion pictures, this area appears to be broken up progressively into smaller and smaller areas, each developing different contraction rates despite continued slowing of conduction. An attempt at static pictorial representation of what moving pictures show clearly is made in Fig. 2.

The fan-shaped lines of Fig. 2*A* serve to denote roughly the slow sweep of contractions from the point of stimulation. If a small rectilinear area such as is drawn in this figure is enlarged, we note a portion of the unidirectional sweep of the wave, as indicated in Fig. 2*C*. If such a small area is studied frame by frame, in moving pictures, we note that, as fibrillation progresses to the convulsive stage, waves begin to travel in different directions at different times, as illustrated in Fig. 1*D*. During the tremulous stage, myriads of minute wavelets seem to spread over this small area, as shown very imperfectly in Fig. 1*E*. Finally, in the atonic stage, waves of contraction spread occasionally and lazily over portions of this area, as indicated in Fig. 1*F*. If several such areas are compared, the tempos of dominant contractions are rarely related; in fact, considerable differences are usually found. Such an analysis of surface contractions by cinematographic methods is probably more precise than a study of contractions recorded by simple mechanical devices, for records so obtained are decidedly affected by shortening and lengthening in adjacent and underlying muscle. Consequently, the evidence presented by Rothberger and Winterberg[16] that the contractions in different regions are synchronous cannot be regarded as convincing. Indeed, Rothberger,[17] in reviewing this work, admits that synchronism of regional contractions is found only occasionally and, we may add, it then probably occurs fortuitously. Evidence of asynchronism

in different regions was also found by B. Kisch,[18] who registered electrical variations by two punctate leads from the ventricular surface. He found that the deflections from such areas differ as to amplitude, form, direction, and number. I have recorded similar, punctate unipolar leads simultaneously from three or four regions of the ventricles, together with a standard electrocardiogram, in fourteen dogs. Analysis of many records has shown that only exceptionally, and for brief periods, is there any synchronism of deflections. Examples are shown in Figs. 3, 4, and 5. Fig. 3 illustrates *four such leads from areas indicated* on the adjacent photograph of the ventricles, while the ventricle was beating normally, just before fibrillation.

Fig. 4 shows the records from the same points during the convulsive stage of fibrillation, i.e., about one minute after the induction of fibrillation. White lines, corresponding to the troughs of the standard electrocardiographic deflections, are drawn to cut the respective curves. A glance shows the lack of incidence, as well as the differences in direction, form, and amplitude, of the most nearly corresponding waves. The tempo and regularity of the major deflections are also variable. Thus, in the segment reproduced as Fig. 4, we can count nineteen to twenty-one waves in the lead from point *1*, twenty-one irregular waves in that from point *2*, thirteen rather regular deflections in the lead from point *3*, eleven variable waves in that from point *4*, and nineteen periodically variable deflections in the standard electrocardiogram (Lead II).

It is difficult to understand how such asynchronism of visible and electrical waves could occur as a result of the release of stimuli from a unitary center or a single excitation ring. This also accords with the evidence on ventricular fibrillation presented by Brams and Katz.[19] On the other hand, it is easy to explain by assuming that a wholly unorganized spread of impulses occurs, and that fields of re-entry are progressively reduced as a result of the interference of more and more impulses.

As the areas diminish in size the convulsive movements are transformed into tremulous vibrations, because the waves re-enter more frequently. The tempo of fibrillation in small areas, and therefore of the whole heart, becomes very rapid. Coincident with this breakdown into smaller areas, the frequency of fibrillating waves in standard leads increases progressively from 500 or 600 to 1,000 per minute, or more. However, variations in the tempo of local, standard, electrocardiographic deflections must be expected because of the frequent summation of the ultimate potential differences which are created by spatially separated fiber groups. Fig. 5 shows 3 punctate leads, together with a standard Lead II, during the early tremulous stage. The calculated frequency of deflection in the upper record is 840/min., in the

second, 675/min., in the third, 600/min., and, in the retouched lower curve, about 480/min.

Another factor enters, however, to explain the progressive changes of fibrillation. During the first three stages, the vigor of contraction is fairly well maintained in individual fractions. This and the frequent excitations probably account for the higher metabolic rate observed

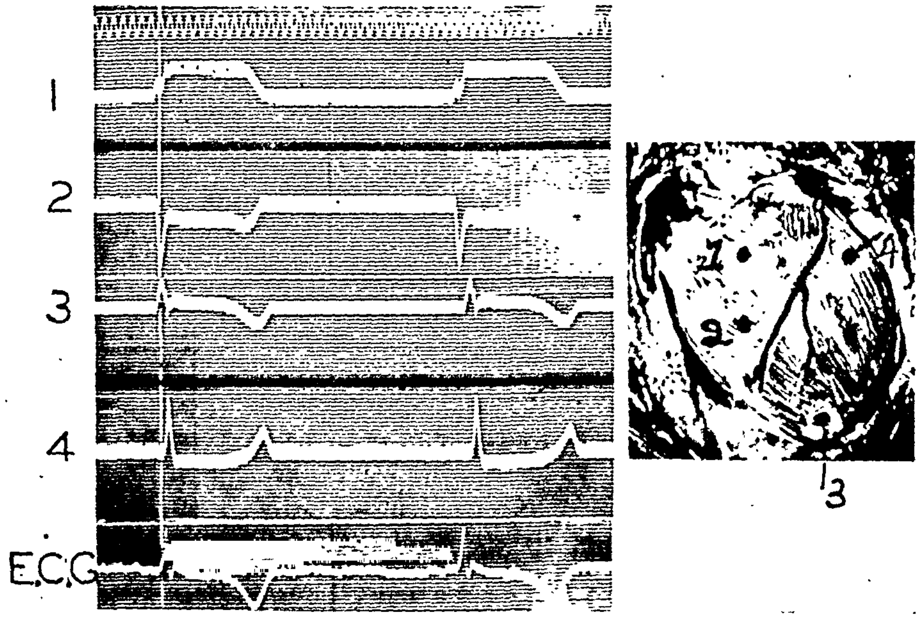

Fig. 3.—Four, punctate, unipolar leads from points on the ventricular surface, indicated by picture of heart, to right, and an electrocardiogram (Lead II) from normally beating heart.

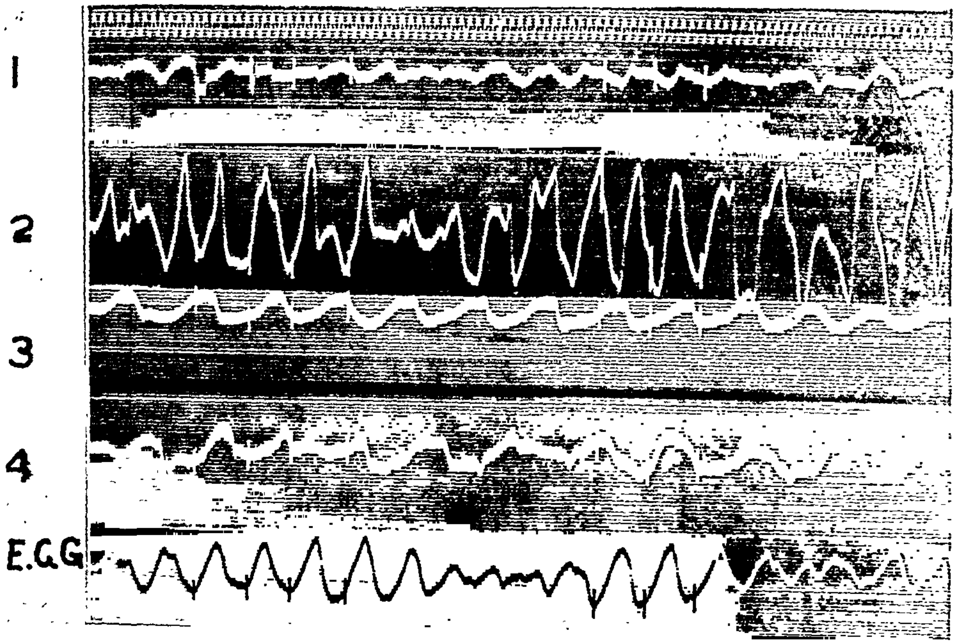

Fig. 4.—Same leads as in Fig. 3, from same heart during convulsive stage of fibrillation, i.e., thirty-nine seconds after its induction.

by Hooker and his associates.[2] However, the only readily available supply of the oxygen which is necessary for contraction is bound to myohemoglobin. The oxygen bound to the blood in the ventricles is probably of little use. As the oxygen is gradually depleted and waste products continue to accumulate because of the absence of circulation, the fractionate contractions become progressively weaker, and finally cease entirely. This explains the ultimate weakening of contractions during the atonic phase of fibrillation, which may last thirty minutes or more.

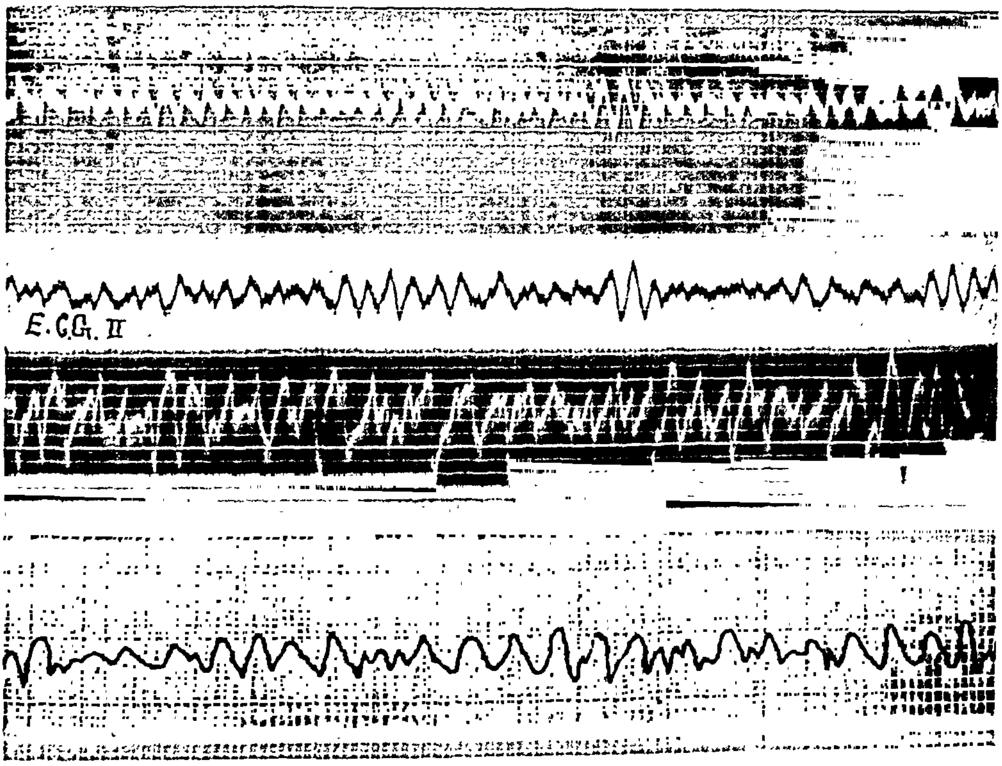

Fig. 5.—Similar leads from another heart during beginning of tremulous stage.

SUMMARY

Ventricular fibrillation, which is a common cause of sudden death following anesthesia, coronary occlusion, electric shock, etc., cannot be adequately described as an asynchronous, incoordinate contraction of ultimate cardiac fractions. The process is an evolution of changes from the moment of its inception until it ceases completely, which is within thirty to forty-five minutes.

The visible spread of waves and punctate unipolar electrocardiograms are reviewed. The available evidence favors the conclusion that, after a single premature systole, the phenomenon is caused by re-entry of circulating wave fronts which involve smaller and smaller blocks of myocardium, each of which develops an independent excitation. As a result of the anoxia which develops progressively after the cessation of coronary flow, conduction is slowed and the vigor of fractionate con-

tractions decreased. The resultant of these changes causes, in succession, the undulatory, convulsive, tremulous, and atonic stages of its evolution.

The theory which best explains these sequential changes and the initiation of fibrillation by the application of a brief, strong, localized shock during the vulnerable period of late systole may be stated briefly as follows:

In order to initiate fibrillation, an electrical stimulus or noxious influences with a "fibrillation threshold" must be applied during the vulnerable period of late systole, at which time certain elements have passed out of the refractory phase. Such a stimulus excites impulses in a number of nonrefractory fractions. These weave their way slowly through local, nonrefractory tissue to form a small wave front, from which a massive excitation wave sweeps over comparatively large portions of the myocardium in sequential order. This constitutes the first premature systole. If the wave front is large enough, and the mode of spread favorable for re-entry at or near, the point of excitation, several circuits are formed through the ventricles; this is the undulatory stage.

In some way—possibly by collision of different excitation fronts, combined with slow conduction—these masses of myocardium are broken into smaller and smaller ones, in which divided waves reenter more frequently. Thus the process passes successively into the convulsive and tremulous stages; during the latter there are innumerable avenues of re-entry. The atonic stage is characterized by progressive enfeeblement of contraction and gradual failure of conduction, which are the result of anoxia caused by cessation of the coronary circulation.

This theory is obviously incomplete in many details and can be expanded only through the development of more perfect methods for following the spread of impulses over the cardiac surface.

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THE PHYSIOLOGIC BASIS FOR CARDIAC RESUSCITATION FROM VENTRICULAR FIBRILLATION—METHOD FOR SERIAL DEFIBRILLATION

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THE high incidence of death from ventricular fibrillation secondary to coronary occlusion and the increasing mortality from accidental electrocution resulting from the widespread use of electrical appliances in our homes, on our farms, and in our trades and professions make the subject of ventricular fibrillation of special interest in the fields of preventive and curative medicine alike. It is obviously imperative that scientists should continue experimentation for the purpose of determining the conditions under which electric currents become dangerous, of attempting to render the ventricles less susceptible to fibrillating agents, and of devising means for the resuscitation of fibrillating hearts. While the rescue of human lives has not yet been achieved, it appears to many that we may be on the threshold of success, certainly in selected cases. However, our hope of crossing that threshold does not lie in the continuance of haphazard modes of experimentation, but in a methodical approach based on an understanding of the physiologic factors which determine success or failure in any given instance.

My own experience has convinced me that the physiologic basis for resuscitation of the ventricles from fibrillation rests firmly on the conception that ventricular fibrillation is not a constant phenomenon, but an evoluting series of changes from the moment of its inception until its natural cessation, which occurs within thirty to forty-five minutes. As was shown in the preceding communication,[1] the asynchronicity and incoordination involve progressively smaller blocks of myocardium, in which the character of the contraction alters as a result of progressive anoxia caused by cessation of coronary flow. Consequently, in devising procedures to defibrillate the heart and to restore normal modes of excitation and vigorous coordinated contractions, we must take cognizance of the state which exists at the time the procedures are applied.

For example, the atonic stage of fibrillation, in which a significant degree of anoxia causes depression of contractile force and slows conduction, develops two to five minutes after the onset of fibrillation, or appreciably earlier than irretrievable failure of the central nervous system. Although fibrillation can be readily stopped at this time, the coordinated beats which redevelop are exceedingly weak and, dynam-

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ically, useless. Consequently, one of the problems of revival consists either in finding means which can be employed within the first three minutes or in devising expedients by which more forceful beats can be restored. Naturally, the use of powerful stimulants, such as epinephrine and related substances, has suggested itself; but it was only realized through considered, fundamental studies that these substances must necessarily prove valueless because they cannot substitute for the oxygen which is lacking.

METHODS OF DEFIBRILLATION AND RESUSCITATION

As Garrey[2] has properly emphasized, the idea of earlier investigators that fibrillation is a terminal process when hearts do not recover spontaneously has been amply disproved by abrogating fibrillation in excised hearts by cooling, by reducing the mass of fibrillating tissue, or by perfusing hearts with potassium chloride solution, followed by Locke's solution. It was, therefore, not entirely unexpected that the prompt use of solutions containing an excess of potassium might likewise abolish fibrillation in the intact heart. Two problems existed, however: (1) to get the potassium ions to the fibrillating ventricle when the circulation is at a standstill and (2) either to remove the excess potassium or to neutralize it with calcium. The former was achieved in 1904 by d'Halluin,[3] who injected KCl solution into a jugular vein and then massaged the heart. Hooker,[4] following an earlier procedure of Crile, introduced a weak solution of KCl into a carotid artery under pressure, while I[5] injected it directly into the ventricular cavities. These various procedures generally proved efficacious in defibrillating the ventricles, and the subsequent use of an excess of calcium sometimes caused a resumption of spontaneous, coordinated beats. Although such occasional recoveries constituted a technical achievement of which we were once justly proud, the therapeutic methods were certainly inadequate. Looking back, they served their chief and broader purpose not in their practical usefulness, but in defining more clearly some of the requirements which must be fulfilled if the attempt at revival is to succeed. These appear to be as follows: (1) Fibrillation must cease completely in every fraction of the myocardium. If even a vestige of fibrillating muscle remains, coordinate contractions never develop. (2) Adequate pacemakers must survive in order to initiate impulses with an excitatory value which is sufficient to inaugurate coordinated contraction. (3) Not too many pacemakers—preferably one—should dominate the re-excitation of the defibrillated ventricle, for if too many act, they cause reversion to fibrillation. (4) The muscle fractions which are so excited must be capable of responding with reasonably vigorous contractions; otherwise, weak, coordinated beats result, and the heart dies in a hypodynamic state or reverts to fibrillation.

As I periodically review my own experiments on the successive use of potassium and calcium, it appears obvious why failures often occurred; indeed, it is remarkable that the method succeeded as often as it did. Potassium abolishes fibrillation, it is true, probably by rapidly depressing conductivity, but it depresses contraction and rhythmicity, as well. When calcium is used subsequently, it may reawaken too many pacemakers, with the result that the ventricles revert to fibrillation. However, if repeated revivals are realized, the animal remains in a prolonged state of hypercalcemia, which serves no good purpose. Epinephrine aids by strengthening the contractions, but it tends to reawaken multiple pacemakers and hence reversion to fibrillation.

A new epoch in resuscitation was opened when Hooker, Kouwenhoven, and Langworthy[6] showed in 1933 that the dog's ventricles can be defibrillated, and natural, coordinated beats restored, by the passage of a 60-cycle alternating current of about one ampere, for 0.1 to 5 seconds, through the heart by means of padded electrodes. Admittedly, they were preceded in this discovery by others (e.g., Prevost and Battelli, 1900), but, as is often the case in the advance of science, the greater credit properly belongs to those who place a discovery on a substantial foundation and thereby give it currency in scientific thought. We at once repeated the experiments of Hooker, et al., with many favorable results, and, by lecture and demonstration, have attempted to acquaint laboratory workers and surgeons with the procedure.

Ferris, et al.,[7] made a further contribution by showing that the method is efficacious for the unexposed hearts of larger animals, provided very strong alternating currents are applied to the chest immediately and briefly, through padded electrodes. However, the method has its limitations. All agree that recovery is rare unless the countershock is applied within the first two or three minutes after electrocution. When the fibrillation is the result of coronary occlusion, countershock is not generally efficacious even within this short period of expectancy.

In our continued use of the method we gradually began to understand the causes for failure and periodically devised slight, but essential, modifications, with the result that with proper technique revival now generally occurs even following coronary occlusion and when the fibrillation has continued for five to ten minutes. In many instances the same heart was revived five to ten times, and we have a banner experiment in which forty-one recoveries occurred in the same dog. These modifications were not haphazard but were suggested by results of other experiments which I shall briefly relate.

First, we noted that when fibrillation had continued five minutes or more, failure to recover was not caused by the fact that the ventricles could not be defibrillated, but by the incapacity of the myo-

cardium to resume vigorous beating. Massage and epinephrine generally caused reversion to fibrillation. Then Tennant and I[8] made the seemingly unrelated discovery that a region of heart muscle which has been totally deprived of its blood supply by coronary occlusion loses its contracting power within about one minute. Similarly, we found that perfusion of the ramus descendens with Locke's solution does not provide a heart which is working in the body with sufficient oxygen to keep the perfused region contracting. Apparently, the fibrillating ventricle which has been deprived of its coronary blood supply similarly loses its capacity for normal contractions within a minute or two, and, when defibrillated after that time, is capable of executing only feeble, frustrated beats. The conditions are still worse when a section of the heart has been ischemic for a time previous to the onset of fibrillation; this partly explains the less favorable effects when the fibrillation is caused by coronary occlusion. Apparently, the indications are to supply the myocardium with oxygenated blood *during the period of fibrillation,* so that, the moment fibrillation is stopped, the muscle can contract vigorously. Accordingly, I[9] suggested, in 1936, that cardiac massage be started as quickly as possible after the onset of fibrillation and be continued until the electrodes are ready to be applied to the heart. By compressing the ventricles manually about forty times per minute, the arterial pressure can be raised to approximately 60 mm. Hg, thereby furnishing oxygenated blood to the heart (*via* the coronaries) and to the central nervous system.

In 1936 I[9] reported the revival of forty dogs from a group of forty-seven, and by 1938 I[10] had records of 168 revivals out of 187 attempts. The procedure has become standard in our laboratory, and its routine use by my associates has contributed significantly to the success of their complicated experiments on the coronary circulation, so that the revivals now number at least 1,000. Recently, we have adopted the procedure of partly compressing the root of the aorta between the fingers occasionally during the manual compression of the heart, in order to send most of the expelled blood through the coronary circuit.

A second cause of failure to revive the heart is the inability to defibrillate the ventricles completely by a single shock. In order to be successful, the alternating current countershock must be very brief and strong. In addition, it must be so applied that a current of effective strength traverses the whole myocardium. In large dog hearts—and this probably applies to human hearts—this is sometimes difficult to accomplish, with the result that a small area continues to fibrillate. Very commonly this is the interventricular septum. Generally, such fibrillation is mirrored by fine movements over the septal region of the anterior ventricular surface, but occasionally no surface activity is apparent, in spite of the fact that the electrocardiogram still shows

small fibrillary waves which are easily modified by changing the position of the heart.

The experiments of Beck and Mautz[12] indicated that the injection of small quantities of metacaine or procaine into the right ventricle before using the massage and countershock is helpful in abolishing such residual areas of fibrillation and hence in restoring normal beating. We do not believe that such an adjuvant action has been crucially demonstrated for these or any other drugs. The observations of Mautz[11] that procaine reduces the irritability of the heart during diastole, and our own confirmatory evidence (unpublished) that the fibrillation threshold is reduced somewhat, do not necessarily have any relation to the ease with which single electric shocks defibrillate the ventricles. When single, strong shocks are used, there is so much variability in their capacity to defibrillate the ventricles that successful defibrillation after the use of procaine does not demonstrate an adjuvant action. In our large experience with the method, it has frequently happened that repeated shocks failed to defibrillate, and, when we were nearly ready to stop our trials, a single shock, to our surprise, became effective. Procaine may have an adjuvant action, but, before this depressant agent is generally used, more substantial evidence of its effectiveness is needed than is furnished by the methods so far devised. In any event, we were not convinced that it helped to restore normal beating, because, like quinidine, it depresses the ventricular myocardium. This was also noted by Beck and Mautz,[12] who then adopted the expedient of improving contractility by additional injections of 5 c.c. of $CaCl_2$ in heparin, a procedure which I originally advocated but have now abandoned for reasons already discussed.

SERIAL DEFIBRILLATION

During the past year Wegria and I have had remarkable success with another modification of the countershock method which we shall call serial defibrillation. This modification consists in applying to the ventricles, through padded electrodes, not one, but a series, of brief and weaker alternating current shocks. Each shock lasts less than one second, and has a strength of approximately 1.0 ampere; one or two seconds elapse between the shocks. As a rule, from three to seven such shocks suffice.

The change in technique is slight, but the effects on the fibrillary process are quite different. Each successive alternating current shock tends to merge smaller fibrillating areas into larger ones, until a convulsive state, involving larger blocks of tissue, is redeveloped. A final shock then stops the fibrillation and allows coordinated beating to be initiated by natural pacemakers. It is our impression, from many observations, that the deeper myocardium and septum are thus included in fibrillating circuits and, in consequence, that these larger

circuits are interrupted without the actual passage of currents through the deeper layers and septum, as is apparently the case with single alternating current shocks which defibrillate. In addition, the likelihood of inducing auricular fibrillation is much reduced, so that another drawback which is inherent in the use of a single, strong countershock is avoided. Since September, 1939, Dr. Wegria and I have recorded 327 revivals out of 328 attempts and have succeeded forty-one times in one dog weighing 15 kilos. In fact, death from fibrillation in dogs with exposed hearts to which serial shocks can be administered within five minutes is evidence of gross negligence.

PRESENT STATUS REGARDING APPLICABILITY

The chief value of the experimental work, so far, consists in the help it gives in orienting ourselves as to the directions in which further research may profitably proceed and as to the avenues of pursuit which appear to be less promising, if not futile. Great as our progress has been during the past two decades, seemingly insurmountable obstacles still prevent an immediate application of our current knowledge to the practical problem of defibrillating the ventricles and restoring forceful coordinated beats after accidental electric shock or coronary occlusion. However, it is as important to face these difficulties as it is to herald our advances, for further approaches can be made only when the problems confronting us are clearly delineated.

In the case of an accidental electrocution in which the patient has been rendered unconscious, pulseless, and apneic, and no heart sounds are audible, the question arises whether the ventricles are fibrillating or the heart is arrested. The latter frequently happens after the passage of very strong currents. The fear has been expressed that the use of countershock in the latter instances might start a fatal fibrillation; whereas, if the patient were left untreated, spontaneous recovery might occur. The suggestion has even been made that any emergency rescue plan should provide for suitable electrocardiographic equipment by means of which the mechanism of the heartbeat might first be ascertained. Personally, I regard this as impractical, useless, and a waste of precious moments. In the first place, there is, at present, *no portable* electrocardiograph which has the two requisites for such "field" use, viz., battery operation and visible recording or electroscopic arrangements. Furthermore, electrocardiograms, if they could be obtained free from skeletal action potentials, might still be indecisive, e.g., in differentiating the waves of ventricular fibrillation from those of auricular fibrillation with ventricular standstill. Finally, complete arrest of the heart is rare, and, if revival has not occurred before an electrographic picture can be examined or before countershock electrodes are put in place, the pacemakers or conducting system are irretrievably damaged, and no spontaneous recovery can be expected.

An important question which arises in relation to human emergencies is. Can sufficient current to defibrillate the ventricles be sent through the human heart by means of chest electrodes? It has been emphasized repeatedly (Hooker, et al.,[6] Ferris, et al.[7]) that, although current durations of 0.1 second suffice and are, indeed, preferable, the current passing through the heart must have a minimal intensity. Thus the minimal amount of current, when applied as one shock by direct electrodes, which will arrest fibrillation in the dog's heart lies between 0.8 and 2.0 amperes. It is therefore improbable that the ordinary alternating current, 110-volt house circuits which are usually available can yield sufficient current to defibrillate human hearts, even when electrodes are applied directly. In order to defibrillate dogs' hearts through chest electrodes, at least six to seven amperes are required, and, in the case of hearts of animals which are comparable in weight to that of man, Ferris, et al.,[7] found it necessary to apply 3,000 volts, which gave currents of twenty-five to 30 amperes. The danger* —not to mention the general unavailability—of such currents for rescue work is apparent.

Our observation that defibrillation can be accomplished in the dog by the successive application of several comparatively weak shocks suggests that further studies ought to be made on larger animals in order to ascertain whether weaker currents might not suffice if the method of serial defibrillation were used.

Even if these vicissitudes were overcome, we would still be in a race with time. To be effective when the chest is unopened, such countershocking currents must be applied within two to three minutes after the onset of fibrillation. Even when all of the equipment is at hand, speed in the execution of each step is required in order to remain within the brief time limits. If apparatus needs to be rushed to the victim, or the victim to the apparatus, attempts to rescue appear to be futile. Consequently, for the present, the chance of success is much greater in the case of patients who are already on the operating table, particularly when the chest has been opened. Such instances of fibrillation should offer the most favorable opportunity for the utilization of countershock, even after the three-minute period. An artificial coronary circulation sufficient to supply the myocardium with oxygen can be created by massaging the heart under aseptic conditions, and the subsequent application of adequate, serial countershocks should cause resumption of vigorous ventricular beating. In such attempts at revival, we should cast aside fetishes of therapy which have been proved experimentally to be unsound. No cardiac stimulant can be of service, for it cannot be expected to benefit an anoxic mammalian myocardium. It can only do harm by setting up

*Burns, injuries to the spinal cord, closure of the epiglottis, and congestion of the trachea and bronchioles are some of the harmful effects which have been noted in reviving such large animals.

multiple foci which tend to cause reversion to fibrillation. Likewise, all agents which are known to modify, or are suspected of modifying, conduction, and, therefore, recovery from fibrillation, probably do more harm than good, because of the fact that they depress an anoxic myocardium still further. There is no substitute for lack of oxygen, and the only known way to deliver oxygen through the coronary channels is by cardiac massage.

But even if the heart be revived, we may still be defeated in our race with time. Experimental evidence indicates that the central nervous system can probably not endure the complete anoxia which results from ventricular fibrillation for more than fifteen minutes, and perhaps not that long. Moreover, the possibility of reviving higher centers through elevation of blood pressure by cardiac massage is not as promising as that of reviving the ventricles, and, in the event of resuscitation, the possibility must be kept in mind that, unless revival is prompt, the recovered victim may be left in a state of mental deterioration.

A word may be added as to the possibility of restoring normal beating after fibrillation secondary to coronary occlusion. The normal dog's heart can rarely be revived unless the occlusion is removed, and this is impossible in man. But even when the vessel is again rendered patent, in experimental animals, revival is difficult unless the ischemic area is first flooded with a supply of arterialized blood through cardiac massage. Unless this is done, the fibrillation may be abolished and the remainder of the heart may beat a few times, but the ventricles quickly revert to fibrillation, probably because the ischemic area, or its margins, develop too many pacemakers.

In conclusion, although the problem of reviving human fibrillating hearts must not be considered hopeless, we must not yet allow ourselves and others to expect too much in a practical way from our present methods until the next fundamental forward step is taken, viz., provision of oxygen for the fibrillating ventricle by methods other than massage. Since we lack suggestions in this direction, it would seem more profitable for the present to direct research talents toward the problem of reducing the sensitivity of the ventricle to the agents which cause fibrillation, with the hope, eventually, of making the heart completely refractory to fibrillation.

SUMMARY

A number of procedures which can be credited with a measure of success in defibrillating the ventricles of dogs and in restoring normal, vigorous beats are reviewed. The physiologic conditions which seem to determine success or failure are analyzed and, based upon this, a modification of the countershock method, called serial defibrillation, which appears to be more uniformly successful, is described.

In dogs with exposed hearts, fibrillation can be stopped and coordinated beats re-established by passing strong alternating currents for brief intervals (0.1 to 5 sec.) through the ventricles, provided such countershock is applied within approximately two minutes. It has been estimated that, in order to achieve similar results in man by applying electrodes to the chest, 2,000 to 3,000 volts yielding currents of twenty-seven to thirty amperes might be needed; so much current would be dangerous to both operator and patient.

Hearts of dogs which have fibrillated for five to fifteen minutes may likewise be revived, provided the ventricles are rhythmically compressed by hand for about one minute previous to the application of the countershock. Frequent inability to revive the ventricles by these procedures is the result of one or more factors: (1) Failure to abolish every trace of fibrillation, (2) failure of natural pacemakers, or conduction, to survive (3) depression of muscle fractions as a result of anoxia, so that they cannot respond with sufficiently vigorous contractions after defibrillation, and (4) the reawakening of too many pacemakers, which cause a reversion to fibrillation through conflicting excitations.

As regards the first difficulty, our recent experimental work indicates that fibrillation can be more certainly abolished in every portion of the ventricle, and by the use of weaker currents, if, instead of one shock, three to seven shocks are applied at intervals of about one or two seconds. Each consecutive shock causes a coarser type of fibrillation, involving larger masses of muscle, until the final shock arrests the fibrillation completely. It is apparently not necessary for such currents to traverse the entire myocardium in order to bring about complete defibrillation. We call the procedure *serial defibrillation*. It is preferable to the use of drugs, such as quinidine, procaine, etc.; the adjuvant defibrillating action of these drugs has not yet been crucially demonstrated, but the fact that they exert a depressing action on contractility is well established.

As regards the second and third difficulties, it has been shown that the viability of pacemakers and of contracting myocardium can be assured by efficient massage which raises arterial pressure, restores coronary flow, and relieves the anoxia. Incidentally, the viability of the central nervous system tends to be maintained. The use of stimulating drugs, such as epinephrine, calcium salts, etc., cannot be expected to benefit an anoxic mammalian heart, and, after reoxygenation, usually sets up multiple pacemakers which tend to cause reversion to fibrillation.

The difficulties of meeting the conditions necessary for the revival of human fibrillating hearts are analyzed. The conclusion is reached that, although such an achievement is not impossible, we cannot anticipate remarkable results in the present state of our knowledge. For the present, it seems most profitable to attempt to discover, through

methodical research, means of rendering the ventricles less sensitive to agents which cause fibrillation, or, even better, wholly refractory to them.

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ESTIMATION OF CARDIOPULMONARY FUNCTIONAL CAPACITY BY MEANS OF OXYGEN DEBT STUDIES

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A RELIABLE objective method of testing the functional capacity of the heart and lungs has been sought by many investigators. Such a test is particularly desirable when shortness of breath or other symptoms are largely, or wholly, subjective. Diagnostic problems involving cardiopulmonary function frequently arise in cases in which there is a controversy regarding an occupational health hazard, or a claim for compensation for disability allegedly caused by occupational exposure.

All investigators agree that such a test would supplement, not replace, any of the usual diagnostic procedures. An adequate history and a careful physical examination are unquestionably of the greatest importance. It is apparent, also, that no test, however valuable, would supplant the sphygmomanometer, electrocardiograph, or roentgenogram of the chest. Nevertheless, some practical clinical procedure or instrument which will measure individual tolerance to physical activity is needed. This paper is the report of our experience with a cardiopulmonary function test originated by Gustav Nylin,[1] of Professor Jacobaeus' Clinic, in Stockholm.

Many so-called "function tests" have been tried. The most common are stair climbing, various kinds of calisthenics, weight lifting, breath holding, etc. All of them utilize some form of exercise which makes demands upon the heart and respiratory system. With certain modifications of apparatus and technique, the cardiopulmonary function test of Nylin[1] has been selected as most satisfactory. This test is concerned with increased oxygen consumption during graduated work (stair climbing). Such increased oxygen utilization has been termed the "oxygen debt" by Hill, Long, and Lupton,[2] and others. In our selection of this test, attention was paid to the often neglected requirement that the work should not exceed in amount or differ in kind from what most persons are accustomed to in normal, everyday life.

APPARATUS

The apparatus (Fig. 1) includes a stairway circuit, reclining chair, Benedict-Roth metabolism apparatus, and metronome. The total height of the stairway circuit is one meter (six steps). The chair, which is arranged for a semireclining position and placed beside the stairway circuit, may be variously adjusted for individual comfort, including headrest and armrests. The metabolism machine includes attach-

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ments for vital capacity measurements and a device for leak-testing which is used routinely in individual metabolism studies. All tests were performed by a single examiner, in a closed room removed from distracting activity and noise.

CLINICAL MATERIAL

Fifty tests were performed on forty-five subjects who were selected at random from the Montgomery Ward Clinics of Northwestern University Medical School. This series comprised thirty-nine men and six women, whose ages ranged from 17 to 71 years. Subjects were classified according to the principal diagnosis, as follows: Group 1, eight cardiopulmonary subjects; Group 2, eight pulmonary subjects; Group 3, thirteen cardiac subjects (without heart failure); and Group 4, sixteen patients without significant cardiac or pulmonary disease. In each case a complete diagnosis was based upon a thorough history and physical examination, together with such laboratory procedures as were indicated. The principal individual diagnoses may later be referred to in Charts 1, 2, and 3. In addition, 2-meter roentgenograms of the chest, electrocardiograms, thorough chemical and cytologic studies of the blood, urinalyses, and blood Wassermann or Kahn tests were done on all subjects.

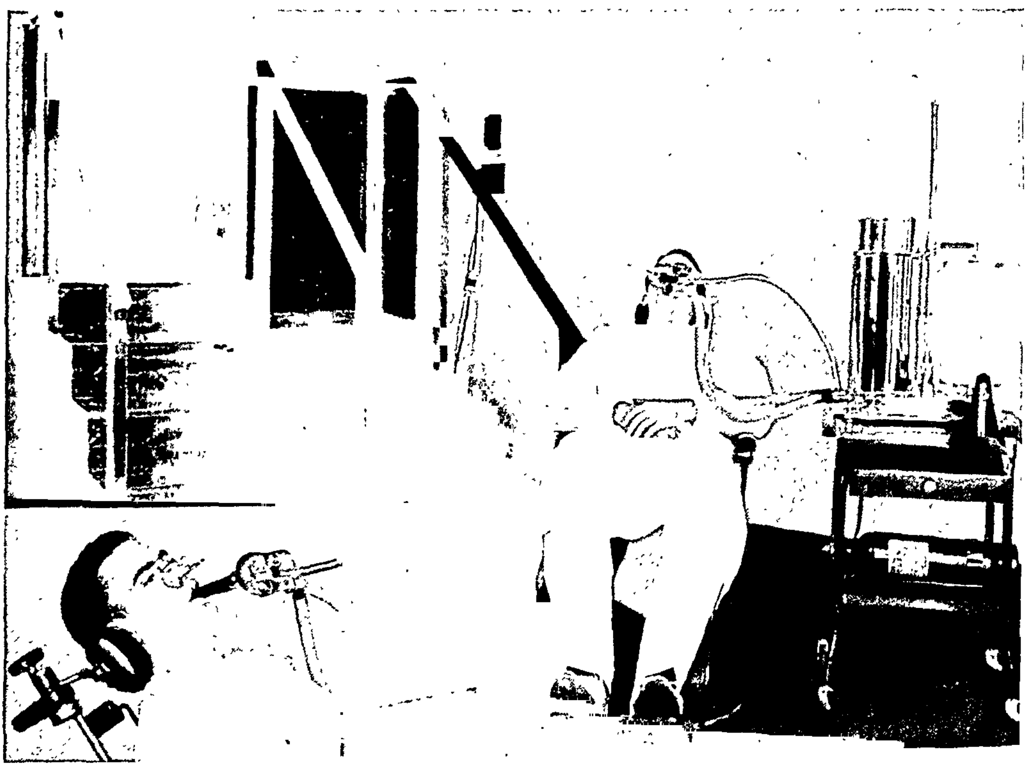


Fig. 1.

METHOD

In an interview preceding the test, a chronologic occupational history, including information concerning current medication and recent or present illness, and a detailed account of the subject's activities during the preceding twenty-four hours, were obtained. Those with fever were not accepted. Likewise, those who had had alcohol, coffee, tea, tobacco, or food within the preceding two hours were rejected. With the subject comfortable in the semireclining position, blood was obtained for cytologic and chemical studies, the arm-to-tongue *circulation time* (Decholin) was ascertained, and *venous pressure measurements* were made, all by one venipuncture. A simple manometer was used to measure venous pressure, and the reference point was the level of mid-thorax. The arterial blood pressure and pulse rate were recorded

at three- to five-minute intervals until a basal level was reached; this was also done with the subject standing, in a manner similar to that previously described by Crampton[3]. After the semireclining position had been reassumed, three vital capacity measurements were obtained.

After the subject had remained in the semireclining position for fifteen to thirty minutes, a "resting" metabolic rate was taken. This served as a control for comparison with subsequent metabolism studies following exercise. The subject was then instructed to climb the stairway circuit ten times, at a rate, regulated by the metronome, of 100 steps per minute. Immediately upon completion of the exercise a second measurement of the metabolic rate was made; this extended from the beginning of the second minute after cessation of exercise to the beginning of the eighth minute. During the first half-minute of the metabolism study the pulse rate and blood pressure were recorded. Approximately twelve minutes after completion of the first exercise test, the second test, requiring twenty trips over the stairway circuit at the rate of 100 steps per minute, was carried out, following which another measurement of the oxygen consumption was made, together with single observations on the pulse rate and blood pressure. These graduated exercise tests were found by trial to be most acceptable and are hereafter referred to as the 10/100 and 20/100 Exercise Tests.

RESULTS

Individual and group responses to the exercise tests are indicated in the form of charts and graphs; in the latter they are expressed as per cent increase of oxygen consumption above the "resting" metabolic level. No detailed correlation of the various conventional diagnostic aids with the cardiopulmonary function tests was attempted; for this a larger number of cases would be necessary.

With the 10/100 Exercise Test (Graph I), the greatest individual and group oxygen debt occurred in Group 1. The amount of oxygen debt decreased progressively through Groups 2 and 3, and was least in Group 4. Group averages are shown. That of Group 4 was but 46 per cent of the average of Group 1, which means that there was a greatly increased oxygen debt in the latter group. In studying the individual responses to the 20/100 Exercise Test (Graph II), it is to be noted that seven subjects were unable to tolerate this amount of exertion (because of dyspnea). Three had both cardiac and pulmonary disease, one had silicosis and pulmonary emphysema, and three had cardiac disease alone.

In this case, therefore, group averages could not be obtained, but it is apparent that the oxygen debt in Groups 1, 2, and 3 was greatly above that in Group 4. Individual and group vital capacity measurements (Graph III) confirmed the long since established observation that pulmonary and cardiac diseases are, in general, attended with reduced vital capacity. Individual exceptions may be noted. Group averages are shown (excluding six female subjects). The average of Group 4 was considerably higher than that of any of the other groups. A spirogram which is typical of individual response to exercise is shown in Fig. 2, with brief clinical notes on the subject of the study. An increase in the respiratory rate and excursion characteristically follows the 10/100 and 20/100 Exercise Tests, and is quite marked with the latter, in which the baseline of the respiratory tracing resembles a parabolic curve.

CHA

SUBJECT			DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE
											Cardiopulmona
S. C.	Age Sex Wt.	54 ♂ 190	Syphilitic and arteriosclerotic heart disease	2	Laborer	Neg. K. Neg. W.	Heart: 20-25% enlarged Lungs: Passive congestion Aorta: Mod. enlarged	Left axis deviation Myocardial damage	2750 c.c.	10.6 cm.	24 se
J. P.	Age Sex Wt.	57 ♂ 157	Rheumatic heart disease Coronary sclerosis	2 B	Laborer	Neg. W. Doubtful K.	Heart: 20-25% enlarged Lungs: Passive congestion Aorta: Dilatation of asc. and desc. aorta	Left axis deviation Moderate myocardial damage	2400 c.c.	7.8 cm.	27 se
M. B.	Age Sex Wt.	58 ♂ 216	Pneumoconiosis Arteriosclerotic heart disease Syphilis		Coal truck driver	Neg. W. Doubtful K.	Heart: 20% enlarged, aortic config. Lungs: Pneumoconiosis Aorta: Normal	Left axis deviation Auricular brillation	2700 c.c.	14.0 cm.	
I. V.	Age Sex Wt.	54 ♂ 180	Cardiovascular syphilis, with aortic dilatation		Laborer	Neg. K. Neg. W.	Heart: 5% enlarged, aortic config. Lungs: Old bilateral tbc. Aorta: Dilat. and sclerosis	Left axis deviation	3300 c.c.	17.6 cm.	
L. K.	Age Sex Wt.	60 ♂ 188	Rheumatic heart disease Arteriosclerosis	2 A	Factory laborer	Neg. K.	Heart: 5-10% enlarged, mitral config. Lungs: Increased density lower ⅓ left lung Aorta: Normal	Auricular fibrillation	2775 c.c.	17.6 cm.	21 s
W. S.	Age Sex Wt.	37 ♂ 123	Rheumatic heart disease	2	Factory laborer	Neg. K. Neg. W.	Heart: 25% enlarged Lungs: Passive congestion Aorta: Mod. enlarged	Myocardial damage	3275 c.c.	24.0 cm.	20 s
J. D.	Age Sex Wt.	69 ♂ 158	Pulmonary emphysema Scoliosis Mild hypertension		Coal miner Laborer	Neg. W.	Heart: Normal size Lungs: Bilateral emphysema Aorta: Normal	Normal for age	3800 c.c.	16.8 cm.	21 s
S. M.	Age Sex Wt.	59 ♂ 162	Pulmonary emphysema Cardiovascular degenerative disease		Molder	Neg. K.	Heart: Right side enlarged Lungs: Emphysema and passive congestion Aorta: Normal	Ectopic beats Digitalis effect Trigeminy	2450 c.c.		

I

	BASAL		ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE, PER CENT	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Subjects										
Reclining	62	125/94	0	0	0	Resting state	+04.4	60	130/98	Note exercise intolerance
Standing	70	138/108				10/100 exer. test	+60.0	90	152/106	
						20/100 exer. test				
Reclining	64	126/78	Cell pack: 43%	Sugar: 67%	0	Resting state	+25.1	64	128/80	
Standing	70	144/94		CO_2: 48.3		10/100 exer. test	+43.9	74	150/74	
						20/100 exer. test	+47.8	66	145/78	
Reclining	84	140/86	Sed. rate 60 min.: 22 mm.	0	Alb. ++	Resting state	+22.2	80	142/90	
Standing	84	146/94				10/100 exer. test	+58.1	84	162/96	
						20/100 exer. test	+73.3	96	180/108	
Reclining	78	136/90	Sed. rate 60 min.: 34 mm.	Icterus index: 10.0	0	Resting state	+09.0	76	138/72	Note exercise intolerance
Standing	90	144/80				10/100 exer. test.	+50.1	100	168/78	
						20/100 exer. test				
Reclining	96	124/88	0	0	Sugar: +	Resting state	+07.4	96	126/90	Note exercise intolerance
Standing	102	136/102				10/100 exer. test	+80.2	140	186/94	
						20/100 exer. test				
Reclining	60	142/28	0	0	0	Resting state	−04.9	60	140/28	
Standing	66	146/30				10/100 exer. test	+39.4	68	154/30	
						20/100 exer. test	+58.9	78	168/32	
Reclining	86	124/78	0	0	0	Resting state	+10.3	86	128/78	
Standing	102	130/86				10/100 exer. test	+47.5	98	136/80	
						20/100 exer. test	+69.0	112	150/78	
Reclining	60	124/66	0	0	0	Resting state	+34.7	56	112/66	
Standing	66	126/66				10/100 exer. test	+68.8	60	140/72	
						20/100 exer. test	+85.1	66	148/78	

CHART 1—

SUBJECT			DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
											Pulmonary
I. B.	Age Sex Wt.	31 ♂ 120	Hydro-pneumothorax, left Psychoneurosis		Factory worker	Neg. K. Neg. W.	Heart: Normal Lungs: Left hydropneumothorax Aorta: Normal	Normal	2150 c.c.	27.0 cm.	18 sec.
A. K.	Age Sex Wt.	56 ♂ 104	Pulmonary emphysema Slight kyphoscoliosis		Laborer No dust exposure	Neg. K.	Heart: Normal Lungs: Bilateral emphysema Aorta: Normal	Essentially normal	2050 c.c.	5.8 cm.	17 sec.
J. H.	Age Sex Wt.	54 ♂ 147	Healed fibrotic pulmonary tbc. (upper right)		Car-loading foreman No dust exposure	Neg. K.	Heart: Normal Lungs: 2 cavities in right apex and fibrosis Aorta: Displaced to right	Sinus tachycardia Essentially normal	4050 c.c.	8.4 cm.	22 sec.
J. B.	Age Sex Wt.	60 ♂ 177	Pulmonary emphysema Healed disseminated pulmonary tbc.		Mechanic Soft stone exposure	Neg. K. Neg. W.	Heart: Normal Lungs: Many calcium deposits, especially upper third Aorta: Normal	Myocardial involvement	2800 c.c.	12.0 cm.	14 sec.
L. S.	Age Sex Wt.	71 ♂ 140	Pulmonary emphysema Arteriosclerosis		Carpenter	Neg. K.	Heart: Right side enlarged Lungs: Bilateral emphysema Aorta: Normal	Minor changes	3900 c.c.	7.8 cm.	22 sec.
T. W.	Age Sex Wt.	49 ♂ 128	Congenital cysts of lungs Malnutrition		Laborer	Neg. K.	Heart: Normal Lungs: Bilateral congenital cysts Aorta: Normal	Essentially normal	2400 c.c.	6.6 cm.	16 sec.
C. D.	Age Sex Wt.	45 ♂ 148	Pulmonary emphysema		Salesman No dust exposure	Neg. K. Neg. W.	Heart: Normal; right side enlarged Lungs: Emphysema Aorta: Normal	Myocardial damage	3400 c.c.		
S. G.	Age Sex Wt.	57 ♂ 192	Silicosis emphysema Chr. bronchitis Scoliosis		Coal miner Steel worker	Neg. K.	Heart: 15% enlarged Lungs: Silicosis and emphysema Aorta: Normal	Myocardial damage	1400 c.c.		

CONT'D

	BASAL		ABNORMAL			METABOLISM				
Subjects	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE, PER CENT	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Reclining Standing	78 100	134/76 140/94	0	0	0	Resting state 10/100 exer. test 20/100 exer. test	−03.6 +29.8 +36.3	70 78 96	138/84 146/88 152/94	Chest pain on inspiration restricted vital capacity
Reclining Standing	78 86	110/60 114/68	0	Icterus index: 10.0	Alb. +++ Hb. +++ WBC: 10-15 RBC: 35-50	Resting state 10/100 exer. test 20/100 exer. test	+53.2 +107.6 +107.6	80 90 94	108/62 160/66 166/70	
Reclining Standing	115 136	126/80 164/112	Sed. rate 60 min.: 39 mm.	0	0	Resting state 10/100 exer. test 20/100 exer. test	+33.7 +54.0 +68.1	108 122 132	158/98 174/96 174/94	
Reclining Standing	86 94	122/86 122/88	Sed. rate 60 min.: 35 mm.	0	Sugar: +	Resting state 10/100 exer. test 20/100 exer. test	+22.3 +36.2 +46.2	84 90 106	122/86 136/92 152/98	
Reclining Standing	62 70	122/74 126/80	Sed. rate 60 min.: 38 mm.	Total chol.: 306	Alb. ++ Casts: 3-4	Resting state 10/100 exer. test 20/100 exer. test	+08.0 +19.7 +62.1	64 70 78	124/78 134/78 140/78	
Reclining Standing	80 100	110/76 112/90	0	0	0	Resting state 10/100 exer. test 20/100 exer. test	+23.7 +40.2 +45.7	74 78 84	114/80 120/82 122/80	
Reclining Standing	76 86	100/58 108/70	0	0	WBC: numerous	Resting state 10/100 exer. test 20/100 exer. test	+10.6 +43.0 +62.0	76 88 91	108/62 122/70 130/66	
Reclining Standing	78 84	104/78 112/90	0	0	Alb. + Casts: 1-2	Resting state 10/100 exer. test 20/100 exer. test	+10.3 +82.2	80 86	106/78 148/88	Note exercise intolerance

CHART

CARDIAC

	SUBJECT		DIAGNOSIS	FUNCTIONAL CLASS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
P. T.	Age Sex Wt.	51 ♂ 148	Generalized arterio-sclerosis	2A	Steam fitter 2 years exposure to flour dust	Neg. W.	Heart: not enlarged. No aortic config. Lungs: normal Aorta: sclerotic. Calcium in wall of aortic arch	Myocardial involvement	2875 c.c.	28 cm.	19 sec.
G. F.	Age Sex Wt.	57 ♂ 118	Syphilitic coronary vascular disease	2A	Boat cook No dust exposure	Pos. K. Doubtful W.	Heart: subnormal size Lungs: normal Aorta: normal	Left axis deviation Minor myocardial damage	2800 c.c.	18.6 cm.	20 sec.
A. D.	Age Sex Wt.	42 ♂ 193	Essential hypertension	I	Office clerk No dust exposure	Neg. K.	Heart: 10% enlarged. Aortic config. Lungs: normal Aorta: normal	Numerous ectopic beats Moderate myocardial damage	4800 c.c.	16.6 cm.	14 sec.
T. S.	Age Sex Wt.	63 ♂ 137	Hypertensive heart disease	I	Teamster Fireman No dust exposure	Neg. W.	Heart: 5-10% enlarged. Aortic config. Lungs: normal Aorta: normal	Left axis deviation Numerous ectopic beats Minimal myocardial involvement	3200 c.c.	15.6 cm.	16 sec.
E. Sk.	Age Sex Wt.	65 ♂ 251	Syphilitic and hypertensive heart disease	2B	Molder and coal yard work	Pos. K. Neg. W.	Heart: 10% enlarged Lungs: normal Aorta: diffuse aneurysm of asc. and desc. aorta	Left axis deviation Minor changes	2750 c.c.	22.6 cm.	24 sec.
E. St	Age Sex Wt.	65 ♂ 124	Arteriosclerotic heart disease with hypertension	2A	Foundry and coal yard work	Neg. K. Neg. W.	Heart: normal size, shape Lungs: Rt. diaph. adhes. and pleural calcification Aorta: normal	Moderate myocardial damage	2100 c.c.	21.4 cm.	18 sec.

2

SUBJECTS

	BASAL		ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING 2ND MINUTE OF METABOLISM TEST	REMARKS
Reclining Standing	72 78	98/70 110/80	Cell pack: 41%	0	WBC: 10-15 per h.p.f.	Resting state 10/100 Exer. test 20/100 Exer. test	+ 8.5 +50.4 +62.6	72 72 80	96/70 120/70 126/74	
Reclining Standing	80 86	96/68 104/80		0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+12.5 +36.0 +67.1	74 68 82	106/80 110/76 122/76	
Reclining Standing	74 78	164/98 166/114	0	0	Alb. + gran. casts 2-3/ h.p.f.	Resting state 10/100 Exer. test 20/100 Exer. test	+11.3 +57.3 +81.7	72 78 86	160/106 180/104 184/102	
Reclining Standing	68 72	124/70 150/82	Cell pack: 43%	0	Sugar +	Resting state 10/100 Exer. test 20/100 Exer. test	+20.7 +55.3 +67.9	64 72 80	154/74 170/74 190/80	
Reclining Standing	84 94	150/70 148/80	0	0	Alb. + +	Resting state 10/100 Exer. test 20/100 Exer. test	+10.8 +34.2 +48.5	80 86 96	148/80 160/82 172/82	
Reclining Standing	72 84	206/130 206/140	0	0	Alb. + gran. casts 6-8/ h.p.f.	Resting state 10/100 Exer. test 12/100 Exer. test	+ 8.0 +33.8 +62.4	66 64 74	198-186/120 224/120 252/122	Note exercise intolerance

CHART 2—

Subject			Diagnosis	Functional Class	Occupational History	Serologic Reactions	2-Meter Chest Roentgenogram	EKG	Vital Capacity	Direct Venous Blood Pressure	Circulation Time, Arm-Tongue
H. M.	Age Sex Wt.	67 ♂ 164¾	Syphilitic aortitis with aortic regurgitation Previous hyperthyroidism		Shipping clerk No dust exposure	Neg. W. Doubtful K.	Heart: 35% enlarged. Aortic config. Lungs: normal Aorta: aneurysm of arch, 14 cm.	Myocardial pathology and coronary disease	3000 c.c.	12.2 cm.	48 sec
O. P.	Age Sex Wt.	68 ♂ 250	Syphilitic aortitis with aortic regurgitation Hypertension	2B	Farmer and laborer Underground mines for two years	Neg. K. Neg. W.	Heart: enlarged to rt. and l. Lungs: normal Aorta: diffuse dilatation of asc. and desc. aorta	Left axis deviation Moderate myocardial damage	2300 c.c.	16.0 cm.	33 se
S. P.	Age Sex Wt.	50 ♂ 203	Syphilitic aortitis	2B	Farmer and laborer No dust exposure	Neg. K. Neg. W.	Heart: enlarged to rt. and l. Lungs: normal Aorta: arch diffusely dilated, 11.5 cm.	Left axis deviation Ant. coronary artery disease Myocardial damage	2700 c.c.	18.6 cm.	35 s
S. B.	Age Sex Wt.	17 ♂ 133	Rheumatic heart disease Mitral insufficiency	I	Delivery boy No dust exposure	Neg. K. Neg. W.	Heart: normal size and shape Lungs: normal Aorta: normal	Right axis deviation Minor changes	2500 c.c.		38 s (?
R. V.	Age Sex Wt.	52 ♀ 123½	Cardiovascular syphilis, with beginning aortic insufficiency Hypertension	2A	Hotel maid Laundress No dust exposure	Pos. K. Neg. W.	Heart: not enlarged Lungs: normal Aorta: diffusely dilated	Left axis deviation Myocardial involvement with coronary disease	2100 c.c.	11.4 cm.	22 s
G. B.	Age Sex Wt.	50 ♀ 192	Essential hypertension	2A	Housewife No dust exposure	Doubtful K. Neg. W.	Heart: normal size and shape Lungs: normal Aorta: normal	Left axis deviation Minor changes	3150 c.c.	17.4 cm.	14 s
F. L.	Age Sex Wt.	49 ♂ 155	Syphilitic aortitis with aneurysm of descending aorta	2B	Farmer, brick work	Pos. K. Neg. W.	Heart: 15-20 % enlarged Lungs: mild congestion Aorta: aneurysm of descending aorta	Left axis deviation Minor changes	3100 c.c.	6.4 cm.	12 s

CONT'D

	BASAL		ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BL. PRESSURE DURING 2ND MINUTE OF METABOLISM TEST	REMARKS
Reclining	68	144/26	0	0	Alb. + + Sugar + Hb. + RBC: 2-3/ h.p.f. WBC: 30-40 h.p.f.	Resting state	+29.1	72	168/26	
Standing	82	126/18				10/100 Exer. test	+79.8	86	198/46	
						20/100 Exer. test	+79.8	80	202/42	
Reclining	52	164/104	Cell pack: 41%	Total chol.: 358 Icterus index: 10.0	Alb. + + Gran. casts: 4-6/ h.p.f.	Resting state	− 4.0	53	164/112	
Standing	60	180/116				10/100 Exer. test	+40.3	72	180/112	
						20/100 Exer. test	+42.4	80	186/120	
Reclining	80	138/94	0	0	Alb. +	Resting state	+10.2	80	156/92	
Standing	84	160/100				10/100 Exer. test	+25.4	84	166/100	
						20/100 Exer. test	+25.4	92	172/104	
Reclining	80	112/80	0	0	0	Resting state	0	76	120/82	
Standing	100	112/90				10/100 Exer. test	+11.0	70	130/94	
						20/100 Exer. test	+17.2	74	112/84	
Reclining	60	166/100	0	0	Alb. + + WBC: 30-40 per h.p.f.	Resting state	+14.5	60	180/108	
Standing	68	182/112				10/100 Exer. test	+40.7	58	206/108	
						20/100 Exer. test	+45.6	78	212/108	
Reclining	92	170/100	0	0	Alb. +	Resting state	+23.7	94	178/100	Note exercise intolerance
Standing	98	208/110				10/100 Exer. test	+51.7	114	216/102	
						20/100 Exer. test				
Reclining	60	112/68	0	0	0	Resting state	+ 6.8	56	112/68	Note exercise intolerance
Standing	68	124/78				10/100 Exer. test	+26.6	60	120/70	
						20/100 Exer. test				

CH

PATIENTS WITHOUT SIGNIFIC

SUBJECT			DIAGNOSIS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME
J. F.	Age Sex Wt.	21 ♂ 152	Detached retina	Clerk	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	5200 c.c.	8.0 cm.	12 s
W. F.	Age Sex Wt.	24 ♂ 172	Left indirect inguinal hernia	Clerk	Neg. K.	Heart: Upper limit of normal size Lungs: Normal Aorta: Normal	Minimal changes	5600 c.c.	20.8 cm.	24 s
V. C.	Age Sex Wt.	29 ♂ 130	Chronic posterior urethritis	Laborer	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	2800 c.c.	13.6 cm.	25 s
F. B.	Age Sex Wt.	61 ♂ 174	Scalp wen Syphilis	Teamster	Pos. K. Neg. W.	Heart: Upper limit normal size Aortic config. Lungs: Sl. fibrosis Aorta: Tortuous	Normal	3675 c.c.	14.4 cm.	14 s
A. L.	Age Sex Wt.	39 ♂ 137	Internal hemorrhoids	Salesman	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3800 c.c.	12.2 cm.	18 s
P. B.	Age Sex Wt.	57 ♂ 130	Indirect inguinal hernia Varicose veins	Clerk	Neg. K.	Neart: Normal Lungs: Right hilar calcification Aorta: Normal	Normal	3600 c.c.	4.0 cm.	17 s
L. S.	Age Sex Wt.	33 ♂ 150	Left ureteral calculus Hernia	Clerk	Neg. K.	Heart: Upper limit normal size Lungs: Normal Aorta: Normal	Minimal changes	3800 c.c.	15.6 cm.	22 s
K. S.	Age Sex Wt.	28 ♂ 141	Chronic gonorrhea Urethral stricture Syphilis	Laborer	Pos. K. Neg. W.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3650 c.c.	12.6 cm.	20 s
B. P.	Age Sex Wt.	26 ♂ 165	Neurodermatitis	Laborer	Neg. W.	Heart: Normal Lungs: Normal Aorta: Normal	Minimal changes	3925 c.c.	13.4 cm.	
O. K.	Age Sex Wt.	36 ♂ 155	Constipation Refractive error	Taxi driver	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	3350 c.c.		

3

CARDIAC OR PULMONARY LESIONS

BASAL			ABNORMAL			METABOLISM		PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BLOOD PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)			
Reclining Standing	84 104	118/76 130/96	0	CO_2: 40%	Casts: 3-5	Resting state 10/100 Exer. test 20/100 Exer. test	+11.7 +14.0 +20.4	82 90 94	120/78 126/80 130/86	
Reclining Standing	66 86	112/70 112/80	0	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+04.4 +17.7 +33.3	68 66 70	112/68 124/76 126/70	
Reclining Standing	62 68	112/80 124/90	0	0	Alb. ++ RBC: many WBC: many	Resting state 10/100 Exer. test 20/100 Exer. test	-04.9 +21.3 +21.3	60 64 66	114/86 134/88 134/80	
Reclining Standing	72	76/56 "Reaction" to decholin?	0	CO_2: 38.4	Alb. + Sugar: + Gran. casts many	Resting state 10/100 Exer. test 20/100 Exer. test	-11.0 +14.6 +23.2	68 72 78	112/70 130/74 138/78	
Reclining Standing	82 96	114/80 120/92	0	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	-02.7 +13.8 +23.5	84 86 96	118/78 126/80 134/82	
Reclining Standing	74 86	114/78 126/86	Sed. rate 60 min.: 25 mm.	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+10.3 +42.1 +42.1	72 76 88	118/78 126/84 132/82	
Reclining Standing	60 84	90/58 100/78	0	0	Alb. ++ Hb. + RBC: 10-15 WBC: 25-30	Resting state 10/100 Exer. test 20/100 Exer. test	+07.5 +11.1 +31.5	62 74 88	108/66 118/78 128/76	
Reclining Standing	68 96	114/74 122/90	0	Sugar: 67 CO_2: 47.4	0	Resting state 10/100 Exer. test 20/100 Exer. test	+12.3 +29.4 +33.0	66 66 72	116/72 126/70 132/76	
Reclining Standing	54 74	118/70 120/85	0	CO_2: 43.7	Alb. ++ Casts: 15-20	Resting state 10/100 Exer. test 20/100 Exer. test	0.0 +33.8 +42.6	54 54 58	118/72 130/70 140/72	
Reclining Standing	62 74	106/70 110/82	0	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	-09.9 +10.9 +18.3	64 58 60	108/72 106/68 108/68	

CHART

SUBJECT			DIAGNOSIS	OCCUPATIONAL HISTORY	SEROLOGIC REACTIONS	2-METER CHEST ROENTGENOGRAM	EKG	VITAL CAPACITY	DIRECT VENOUS BLOOD PRESSURE	CIRCULATION TIME, ARM-TONGUE (DECHOLIN)
J. A.	Age Sex Wt.	47 ♂ 145	Central nervous system syphilis Optic atrophy	Laborer	Pos. K. Neg. W.	Heart: Normal Lungs: Normal Aorta: Slightly widened	Normal	2800 c.c.	6.4 cm.	12 sec.
C. H.	Age Sex Wt.	50 ♂ 144	Questionable mitral regurgitation	Salesman	Neg. K.	Heart: Normal Lungs: Sl. emphysema Aorta: Prominent ascending portion	Minimal changes	3100 c.c.	12.7 cm.	23 sec.
A. S.	Age Sex Wt.	30 ♀ 98	Hay fever	Housewife	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Normal	2450 c.c.	6.8 cm.	12 sec.
M. S.	Age Sex Wt.	45 ♀ 128	Psychoneurosis Scoliosis	Factory worker	Neg. K.	Heart: 15% enlarged, config. uncertain Lungs: Normal Aorta: Normal	Normal	3100 c.c.	6.6 cm.	14 sec.
L. H.	Age Sex Wt.	38 ♀ 155	Uterine fibroids Tertiary syphilis	Housewife	Neg. K. Neg. W.	Heart: 5-10% enlarged, aortic config. Lungs: Normal Aorta: Normal	Normal	2650 c.c.	16.0 cm.	12 sec.
M. F.	Age Sex Wt.	37 ♀ 128	Chronic cholecystitis	Factory worker	Neg. K.	Heart: Normal Lungs: Normal Aorta: Normal	Minimal changes	2750 c.c.	7.2 cm.	12 sec.

Detailed individual studies are presented in Charts 1, 2, and 3. The response of the pulse rate to exercise was found to be variable in all groups. According to Katz, et al.[4] "it is well known that the reaction of the cardiac rate and blood pressure to exercise may show wide variations, even in normal persons." We found that their use as a criterion of response to exercise was particularly unreliable in many of our subjects who had auricular fibrillation or premature systoles, and when there was apprehension or anxiety. In one subject (O. K., Group 4), a moderate decrease in pulse rate was accompanied by a slight fall in blood pressure. A study of basal pulse rates and blood pressures in the semireclining and standing positions revealed no marked deviation from the normal variations described by Crampton. When the vital capacity was subnormal, there was usually an increased oxygen debt, and vice versa, although several exceptions may be noted.

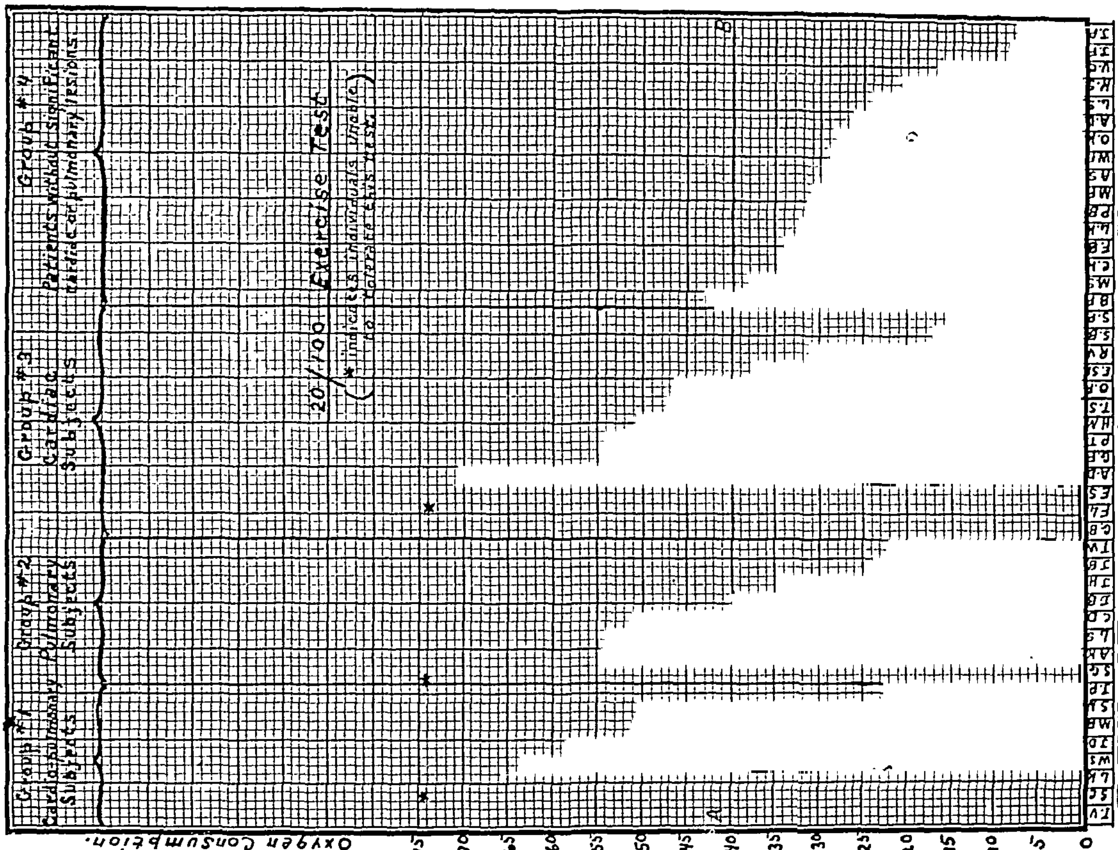
3—CONT'D

	BASAL		ABNORMAL			METABOLISM				
	PULSE RATE	BLOOD PRESSURE	BLOOD CYTOLOGY	BLOOD CHEMISTRY	URINALYSIS		METABOLIC RATE (%)	PULSE RATE DURING FIRST MINUTE OF METABOLISM TEST	BLOOD PRESSURE DURING FIRST MINUTE OF METABOLISM TEST	REMARKS
Reclining Standing	62 76	96/66 110/80	0	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+10.6 +11.9 +18.3	60 60 72	100/70 108/68 112/70	
Reclining Standing	52 64	90/62 106/78	0	0	Alb. +	Resting state 10/100 Exer. test 20/100 Exer. test	+08.8 +18.1 +43.3	50 52 60	102/70 110/70 116/68	
Reclining Standing	70 80	94/60 104/70	Hb: 12.6 Gm. Cell pack: 39.0% Vol. index 1.09	0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+22.6 +52.4 +52.4	72 66 90	94/64 108/60 110/64	
Reclining Standing	72 84	126/78 138/94	Cell pack: 43.0% Col. and vol. index: 1.07	CO_2: 43.6	0	Resting state 10/100 Exer. test 20/100 Exer. test	+16.6 +51.5 +54.6	84 66 74	126/86 130/78 132/72	
Reclining Standing	76 86	110/78 118/80	0	Icterus index: 10.0	0	Resting state 10/100 Exer. test 20/100 Exer. test	+14.2 +30.0 +46.7	76 78 86	114/76 124/80 128/76	
Reclining Standing	84 120	106/64 96/80	0	CO_2: 38.4	0	Resting state 10/100 Exer. test 20/100 Exer. test	+16.9 +46.4 +47.9	76 88 102	112/76 120/76 126/74	

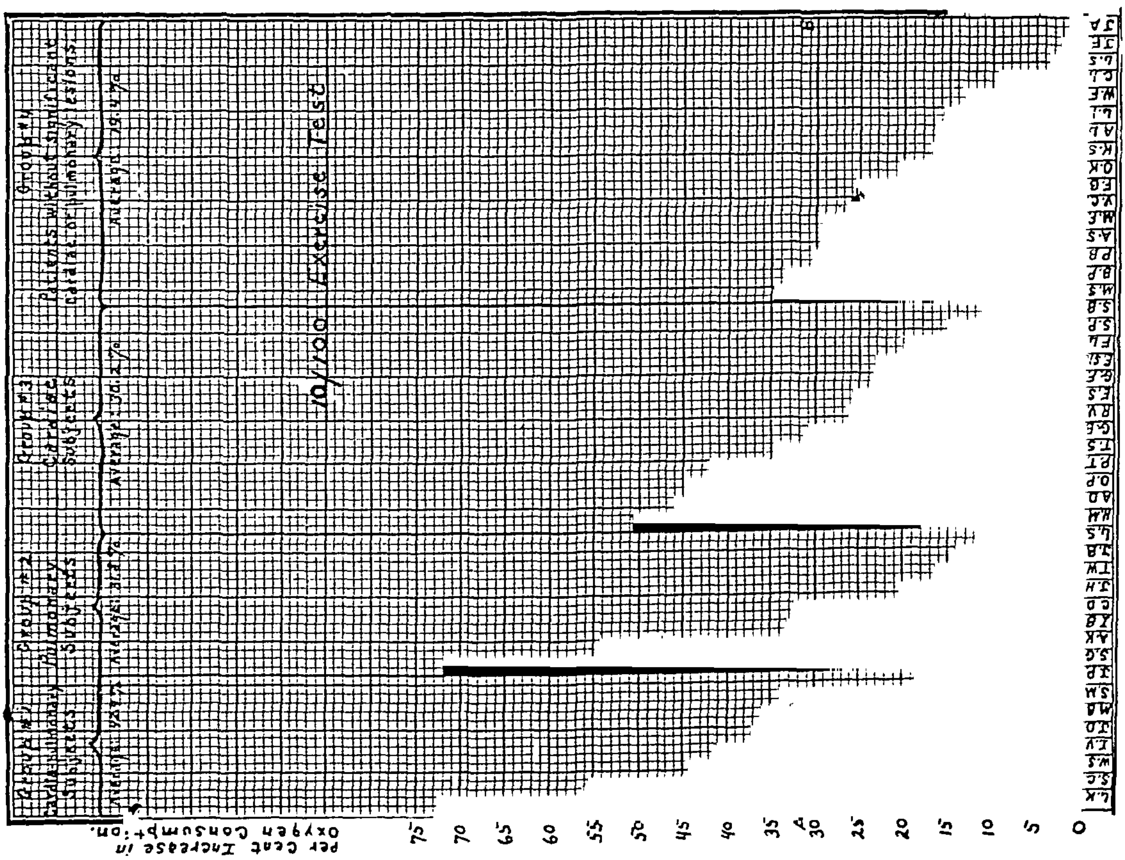
Repeat exercise tests (Chart 4) were done on five subjects representing Groups 1, 3, and 4. When the results of the repeat test are compared with those of the original test, a significant uniformity of response is apparent. Arnett and De Orsay,[5] and others, have pointed out how variable the vital capacity is, and conclude that measuring it is principally useful for making comparisons from time to time in the same patient. The results of our repeat cardiopulmonary function tests indicate, likewise, that comparison of two or more tests on one subject is of greater value than the results of any single test, for individual responses, even in a selected series of single tests, are rather widely variable.

COMMENT

The weak link in any cardiopulmonary function test is its interpretation. The best that can be hoped for in using such a test is to obtain

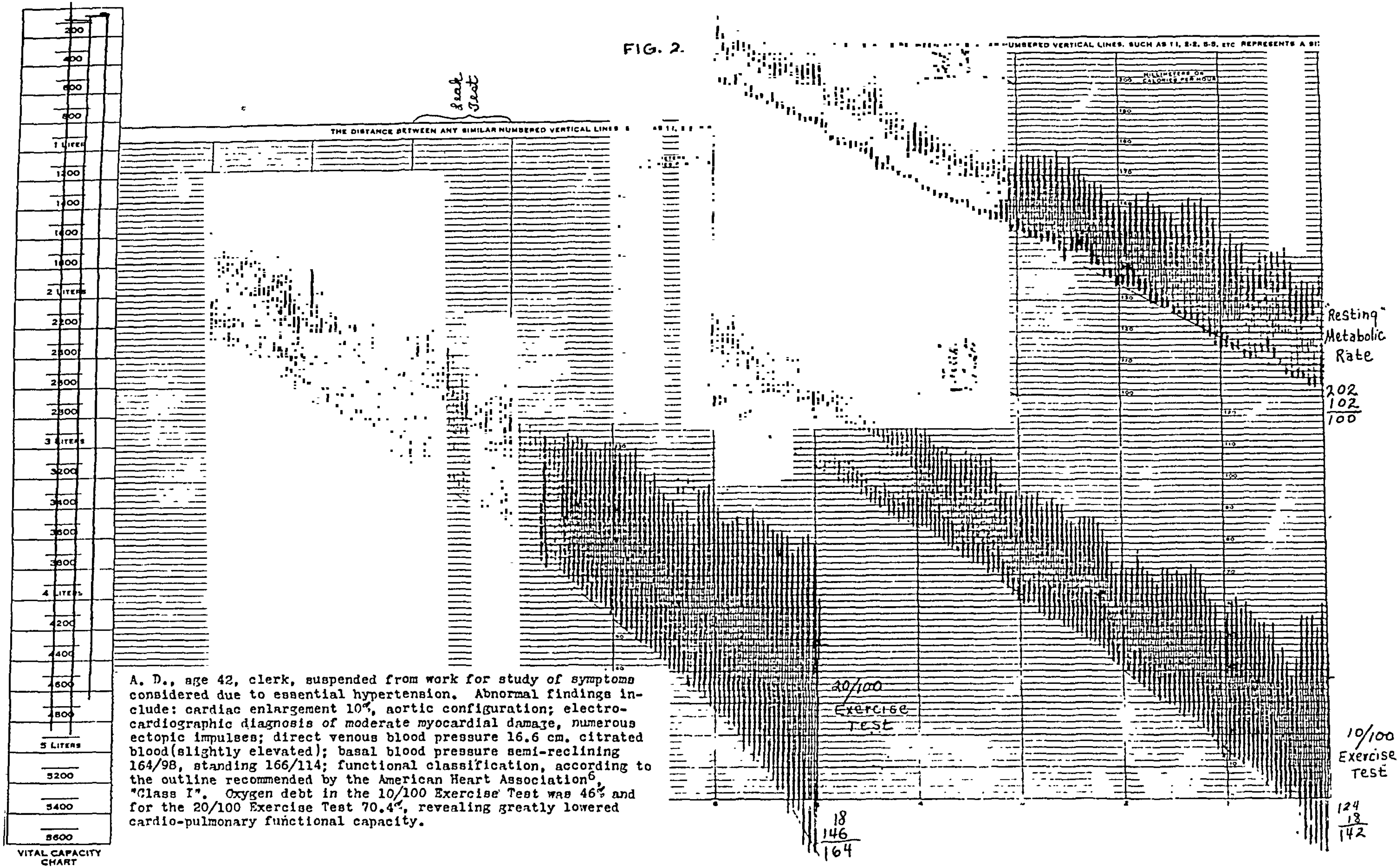


Graph II.



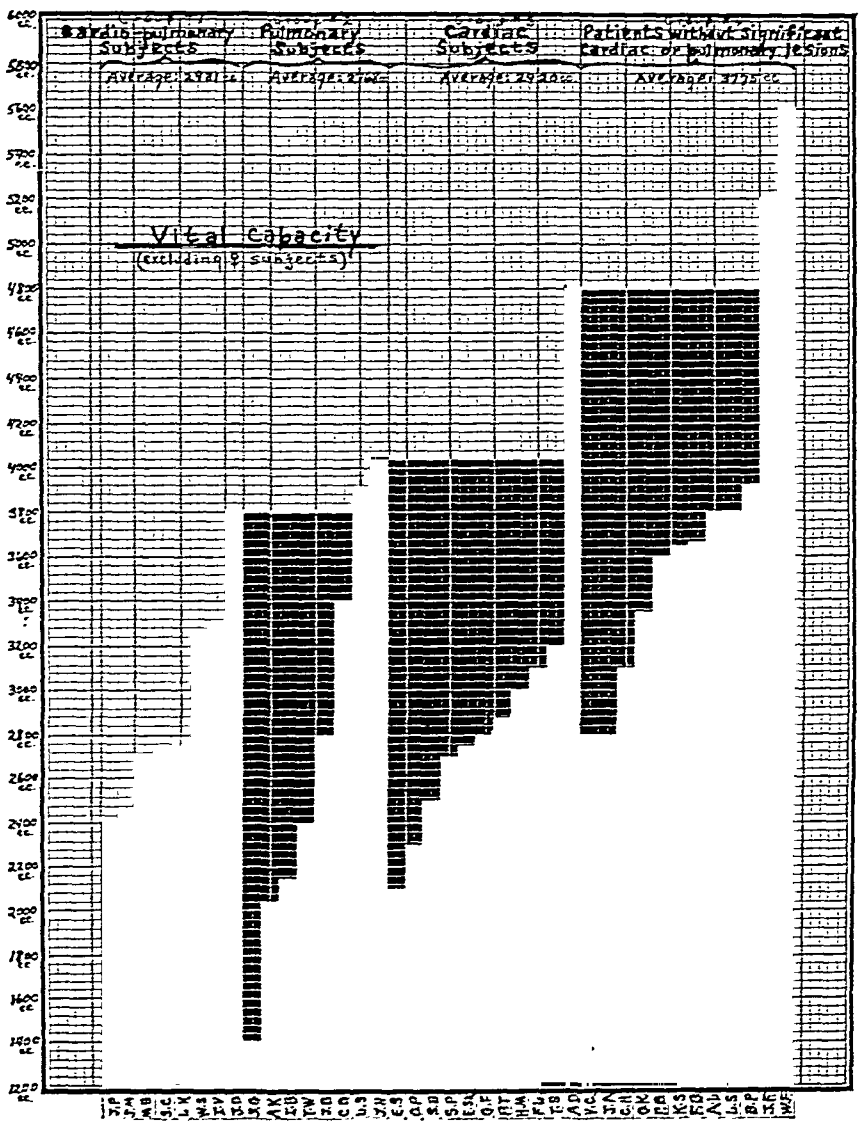
Graph I.

FIG. 2.



A. D., age 42, clerk, suspended from work for study of *symptoms* considered due to essential hypertension. Abnormal findings include: cardiac enlargement 10%, aortic configuration; electrocardiographic diagnosis of moderate myocardial damage, numerous ectopic impulses; direct venous blood pressure 16.6 cm. citrated blood(slightly elevated); basal blood pressure semi-reclining 164/98, standing 166/114; functional classification, according to the outline recommended by the American Heart Association[6], "Class I". Oxygen debt in the 10/100 Exercise Test was 46% and for the 20/100 Exercise Test 70.4%, revealing greatly lowered cardio-pulmonary functional capacity.

a reliable indication of the subject's ability to tolerate work at the time the work is performed. In many instances, no prognosis can be made from the results obtained. In the evaluation of tests involving measurements of the metabolic rate, it is essential to control, as much as possible, factors which may give rise to misleading results. The preliminary preparation of our subjects included an intensive search for factors which might affect the metabolism studies adversely. In addition, the age, sex, state of nutrition, and occupational history were considered in each case. The type of test which we used requires a measurable



Graph III.

expenditure of energy at a definite rate. Faster rates were found to be unreliable. Many "effort" tests, such as hopping, calisthenics, and stair climbing, without accurate timing, do not stress the important factor of uniformity of response. One subject may respond with vigor, and another in a lazy manner. This raises the question of variation in the amount of energy expended. The use of the metronome assures one of

CHART 4

REPEAT EXERCISE TESTS

SUBJECT	AGE	DATE	BASAL METABOLIC RATE			VITAL CAPACITY	REMARKS
			RESTING STATE	10/100 EXERCISE TEST	20/100 EXERCISE TEST		
1. W. S.	37	8/29/39	−04.9%	+39.4%	+58.9%	3275 c.c.	Cardiopulmonary.
W. S.	37	8/31/39	−05.1%	+39.1%	+58.6%	3025 c.c.	No significant interval history.
2. M. B.	58	8/24/39	+22.2%	+58.1%	+73.3%	2700 c.c.	Cardiopulmonary.
M. B.	58	8/31/39	+29.6%	+72.2%	+90.4%	2850 c.c.	More dyspnea at rest. Longer rest necessary for basal pulse rate.
3. V. C.	29	6/22/39	−04.9%	+21.3%	+21.3%	2800 c.c.	Pt. without cardiac or pulmonary disease.
V. C.	29	9/ 5/39	−10.5%	+31.9%	+31.9%	3100 c.c.	No significant interval history.
4. K. S.	28	6/22/39	+12.3%	+29.4%	+33.0%	3650 c.c.	Pt. without cardiac or pulmonary disease.
K. S.	28	8/17/39	+05.0%	+35.2%	+38.8%	3600 c.c.	No significant interval history.
5. G. F.	57	6/ 1/39	+12.5%	+36.0%	+67.1%	2800 c.c.	Cardiac.
G. F.	57	8/31/39	+09.3%	+41.8%	+62.5%	2900 c.c.	Severe precordial pain 2 weeks earlier.

a uniform response. The variability of pulse rate and blood pressure following exercise causes one to question the results of tests which are based solely upon such observations. Any test in which the subject is required to do work is influenced not only by the functional capacity of the heart, but also by extracardiac factors, prominent among which are the respiratory functional capacity and the physical fitness of the subject. It has been our observation that in most instances it is difficult to carry out a test of cardiac function which does not, at the same time, constitute a test of pulmonary function. Hence, the term "cardiopulmonary function test" appears correct.

It is obviously difficult to define a standard of accomplishment for any particular group of subjects. A wide range of variation for normal persons must necessarily be adopted. The lines *A—B* in Graphs 1 and 2 represent arbitrary "upper limits of normal." Conservative opinion suggests that a given response should be considered abnormal only if the oxygen consumption increase exceeds this "limit" by 10 per cent. Attention is again drawn to the advantage of comparing tests made on the same person from time to time.

SUMMARY

The response of forty-five persons with, or without, cardiac, pulmonary and combined cardiopulmonary disease to a modified stair-

climbing exercise test has been studied, and the "oxygen debt" measured.

The results have been compared with those of other types of function tests, and the limitations of interpretation pointed out.

Although the series of cases is small, the results indicate that the test is important as an objective method of evaluating diminution in cardio-pulmonary reserve.

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THE COMBINED USE OF OUABAIN AND DIGITALIS IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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A METHOD of digitalization which will rapidly produce an effective therapeutic concentration of the drug in the body, and maintain this level thereafter, is presented.

Theoretic considerations concerning the production of complete digitalization with the accepted, rapid methods are represented schematically in curves *A* and *B*, of Fig. 1. When a single dose of digitalis is given by mouth, there is a definite latent period of two to five hours before any effect is apparent,[1, 2, 3] and it takes six hours for the maximum effect to develop (see curve *A*, Fig. 1). When doses are repeated according to the method of Eggleston,[4] the full therapeutic effect is not manifest before twelve to twenty-four hours.

The disadvantages of the oral use of digitalis are: (1) the length of the latent period before any effect, or the therapeutic one, becomes apparent and (2) the necessity of repeating smaller doses under careful supervision in order to produce complete and safe digitalization. Its advantage is the slow rate of elimination from the body, which allows persistence of its action for as long a period as ten to fourteen days, and facilitates the establishment of a maintenance dose.

Ouabain (g-strophanthin), when administered intravenously, as demonstrated by Wyckoff and Goldring,[5] exerts an "initial effect in from five to twenty minutes, and a maximum effect in from fifteen to fifty minutes" (see curve *B*, Fig. 1). By giving an initial dose of 0.5 mg. of ouabain intravenously, and doses of 0.1 mg. at intervals of one-half to one hour thereafter, complete digitalization can be obtained in from one and one-half to three hours. Although the action of ouabain is rapid, it has the disadvantage of being eliminated quickly.[5, 6] Because of the fact that we do not know how much of the glucoside there is in the body twenty-four hours after its administration, the dose of digitalis which is necessary to maintain the desired effect is difficult to ascertain.

We have attempted to avoid the disadvantages of both drugs by supplementing and maintaining the early action of ouabain by the simultaneous administration of a single dose of digitalis. It was to be expected that at the time when the therapeutic effect of the ouabain passed its maximum and started to diminish, the slowly increasing

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action of the digitalis would become manifest (see curve C, Fig. 1), and that there would be no interval between complete digitalization and the establishment of a maintenance dosage of digitalis.

This principle, whereby a desired therapeutic effect is obtained quickly with a rapidly absorbed drug, and thereafter maintained with a drug which is more slowly absorbed and excreted, has been applied, also, in the field of anesthesia, and more recently, by Sollmann and his coworkers,[7] to antisyphilitic therapy with bismuth preparations.

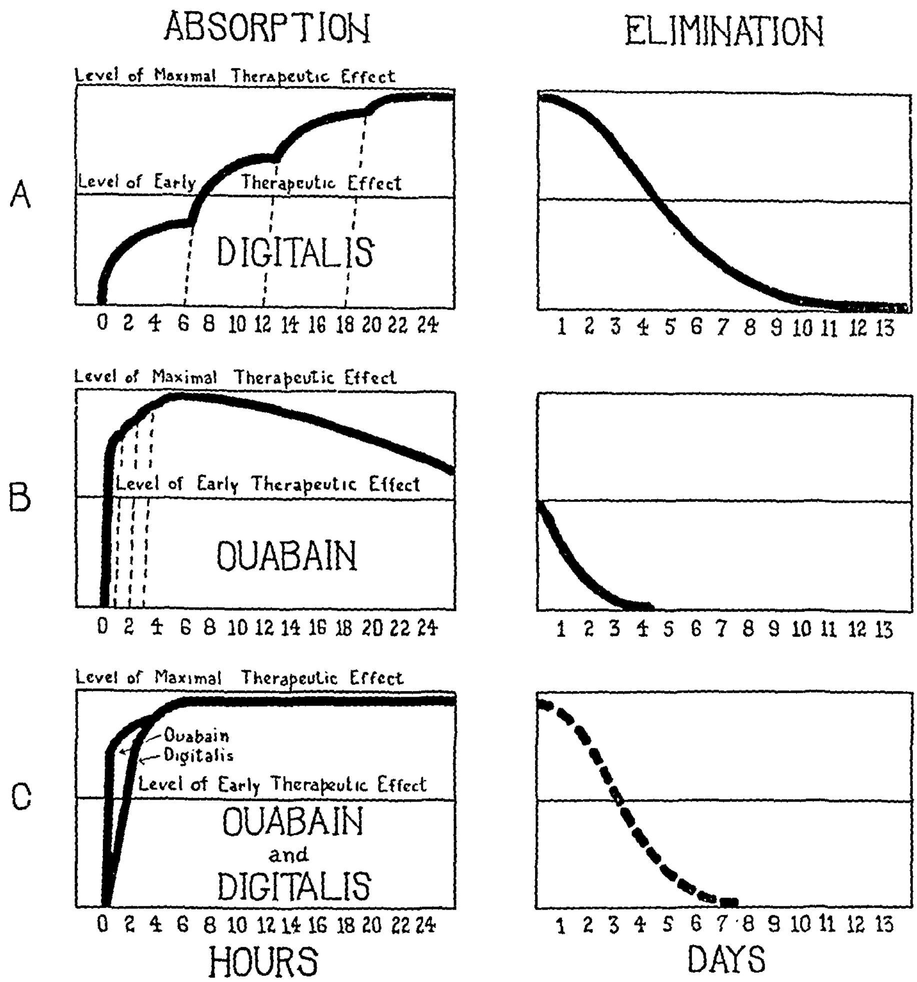

Fig. 1.—Schematic representation of absorption and elimination, *A*, of Digitalis leaf, given orally by method of Eggleston, *B*, ouabain, given intravenously by method of Wyckoff and Goldring, and *C*, digitalis and ouabain in combination. (By elimination is meant the persistence of digitalis effect upon the ventricular rate of patients with auricular fibrillation). The curve of "Elimination" in *C* (broken line) is at present under investigation.

SELECTION OF MATERIAL

Patients were selected as follows: (1) Only those patients whose heart disease could be classified etiologically in accordance with the criteria[8] established by the New York Heart Association were included. (2) During the period of hospitalization the patient must have had some or all of the following evidences of congestive heart failure: dyspnea, orthopnea, congestion of the lungs, a palpable liver, accumulation of fluid in body cavities, or peripheral edema. (3) Patients with recent myocardial infarction were excluded except in two instances. (4) Patients who had received

digitalis within the previous two weeks were excluded. (5) Patients with paroxysmal arrhythmia, but without congestive heart failure, were not included. (6) It was necessary that all patients treated be cooperative, and capable of taking medication by mouth and of giving information regarding subjective changes.

As is seen in Table I, all etiologic types of heart disease were treated, regardless of rhythm, bundle branch block, valvular deformity, or degree of congestive heart failure. The ages of the patients ranged between 28 and 79. Eight patients with myocardial infarction were studied, but, as has already been mentioned, only two had had recent infarction.

The severity of the congestive heart failure in each case, prior to digitalization, was estimated by taking into account (1) the general appearance of the patient, i.e., the degree of dyspnea, orthopnea, and extent of edema, (2) how the patient responded during the preliminary control period, and (3) the opinion of the ward physicians, who made their observations entirely independently.

METHOD OF STUDY

Before digitalization, the maximum effect of absolute rest in bed, the administration of oxygen and sedatives, limitation of fluid intake, and dietary restrictions was ascertained in each case. In seven cases, the preliminary period of observation was omitted because immediate digitalization was considered necessary. Ventricular rates, pulse rates, and blood pressures were recorded daily. At least one electrocardiogram was taken shortly before digitalization began. All patients, with the exception of the two who had recent myocardial infarction, were weighed daily. The weight curve was an excellent guide for following the course of the patient's illness. When the weight remained constant, or when there was an increase in weight during the preliminary control period, rapid digitalization by the combination of ouabain and digitalis leaf was instituted.

When this state had been achieved, 0.5 mg. (5 cat units) of ouabain was given intravenously simultaneously with six or eight cat units of digitalis leaf orally; the amount of the latter depended on the estimated edema-free weight of the patient. No other digitalis was given for twenty-four hours. At the end of this time the patient was placed on a daily maintenance dose of one to two cat units of digitalis leaf by mouth. It is important that only reliable preparations* of ouabain and digitalis be used. Ouabain in solution undergoes deterioration, and, unless a recently standardized preparation is used, the desired immediate effect of a dose which is considered adequate will not be obtained.

Immediately preceding digitalization, ventricular rates, pulse rates, and blood pressures were recorded repeatedly, until constant levels had become established. Ouabain and digitalis were then administered, and the above observations were continued at fifteen-minute intervals for a period of two hours. Electrocardiograms were taken twenty-four hours later, and at frequent intervals thereafter. In five cases, in which auricular fibrillation was present, electrocardiograms were taken at fifteen-minute intervals during the first two-hour period of observations.

All patients were observed daily for symptoms and signs of digitalis toxicity, evidences of improvement, and changes in weight, blood pressure, and ventricular and pulse rates.

Both subjective and objective evidences were used as criteria for improvement. During the first two hours of constant observation, improvement was judged by the general appearance of the patient, decrease in dyspnea, lessening or disappearance of orthopnea, diminution of restlessness and agitation, as shown by drowsiness and the occurrence of sleep, increase in pulse pressure, improvement of the pulse volume,

*Ampules of ouabain, in a concentration of 2.5 cat units per c.c., and tablets of digitalis (whole leaf) of multiple cat unit strength were supplied by Carroll Dunham Smith Pharmacal Company, of Orange, N. J. The potency of these preparations was confirmed in our laboratory by the Hatcher and Brody method of assay.

TABLE I

CARDIAC DIAGNOSIS AND DEGREE OF CONGESTIVE FAILURE

DIAGNOSIS	NUMBER OF CASES	NORMAL RHYTHM	AURICULAR FIBRILLATION	BUNDLE BRANCH BLOCK	MYOCARDIAL INFARCTION	AORTIC INSUFFICIENCY	FAILURE			
							∓	+	++	+++
Arteriosclerotic	17*	16*	1	4	7		4	4	6	3
Hypertensive	10	10		1			2	2	4	2
Arteriosclerotic and Hypertensive	16	13	3	2	1		0	3	10	3
Rheumatic	11	4	7	1		5	1	4	4	2
Syphilitic	3	3				3	2	0	0	1
Rheumatic and Hypertensive	1	1					0	1	0	0
Syphilitic and Hypertensive	1	1				1			1	
Hyperthyroid	1		1				1			
Total	60*	48*	12	8	8	9	10	14	25	11

*One patient treated on two admissions.

TABLE II

RELATION OF TIME OF ONSET OF IMPROVEMENT TO TYPE OF HEART DISEASE

DIAGNOSIS	NO. OF CASES	NUMBER OF PATIENTS IMPROVED IN				
		15 MINUTES	1 HOUR	2 HOURS	24 HOURS	NONE
Arteriosclerotic	17*	3 (17.7%)	6 (35.3%)	3 (17.7%)	5 (29.4%)	
Arteriosclerotic and hypertensive	16	5 (31.2%)	4 (25%)	2 (12.5%)	5 (31.2%)	
Hypertensive	10	5 (50%)	2 (20%)	3 (30%)		
Rheumatic	11	3 (27.2%)	7 (63.6%)	1 (9%)		
Syphilitic	3	1	1	1		
Rheumatic and hypertensive	1					1
Syphilitic and hypertensive	1			1		
Hyperthyroid	1	1				
Total	60*	18 (30%)	20 (33.3%)	11 (18.2%)	10 (16.6%)	1 (1.6%)

*One patient treated on two admissions.

disappearance of gallop rhythm, if it had been present prior to treatment, and, in patients with auricular fibrillation, slowing of the ventricular rate and disappearance of the pulse deficit. Subjective evidence in the absence of objective signs was not considered of major importance. It consisted of the patient's statements with regard to ease in breathing and lessening or disappearance of precordial and epigastric distress. Criteria for improvement at the end of twenty-four hours were the same, and, in addition, consideration was given to decrease in amount of edema, as judged by the weight curve.

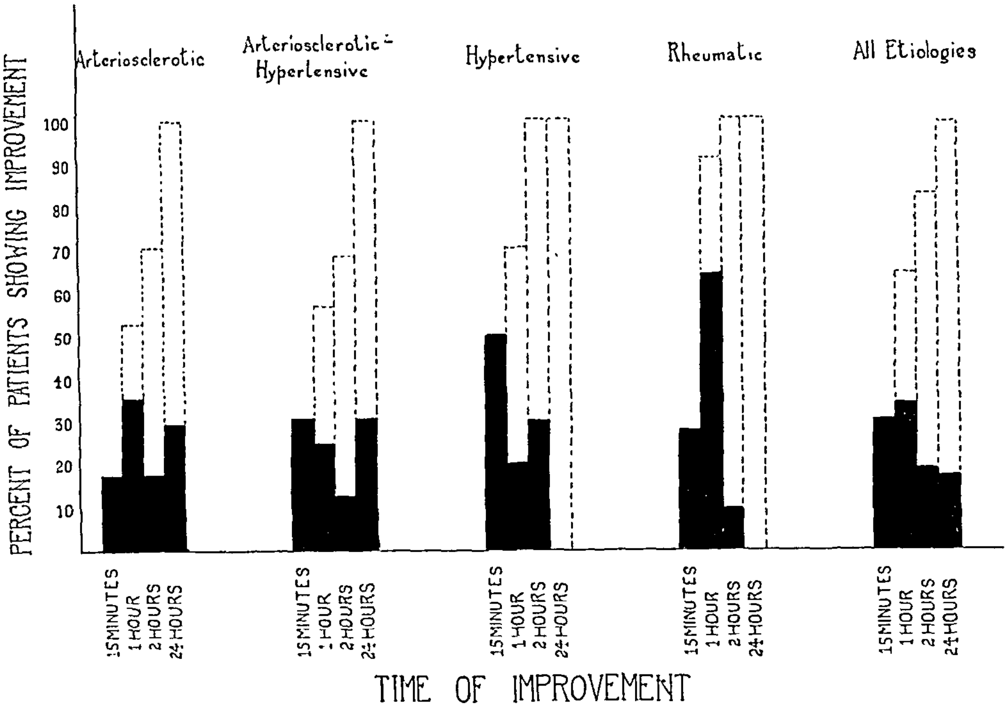

Fig. 2.—Time of onset of improvement in relation to type of heart disease.

RESULTS

In Table II and Fig. 2, the results as to time of onset of improvement in relation to the type of heart disease are summarized. Digitalization was produced sixty times in fifty-nine cases. One patient was treated on two occasions. Improvement was noted within fifteen minutes in eighteen (30 per cent) of the sixty trials, within one hour in thirty-eight (63.3 per cent), and within two hours in forty-nine (81.7 per cent). Improvement, therefore, occurred very rapidly in the majority of the cases. As a rule, this improvement, once established, was progressive, so that the maximum effect of digitalization occurred at twenty-four hours. The only exception was the patient with hyperthyroidism and auricular fibrillation, who, in spite of immediate improvement, with slowing of the ventricular rate from 138 to 90 per minute within one and one-half hours, had lost the effect at the end of twenty-four hours.

It is evident from Table II and Fig. 2 that the type of heart disease determined, to a large extent, the time when improvement first mani-

fested itself. With one exception, all of the rheumatic patients showed improvement within one hour. The early improvement in this group may be explained by the fact that so many of the patients had auricular fibrillation. All patients with hypertension, uncomplicated by arteriosclerosis, were improved within two hours. However, when arteriosclerosis was an etiologic factor in the heart disease, in only approximately 70 per cent of the patients was improvement noted within the first two hours.

TABLE III

RELATION OF TIME OF ONSET OF IMPROVEMENT TO TYPE OF CARDIAC MECHANISM

MECHANISM	NO. OF CASES	NUMBER OF PATIENTS IMPROVED IN				
		15 MINUTES	1 HOUR	2 HOURS	24 HOURS	NONE
Auricular fibrillation	12	3 (25%)	7 (58.3%)	1 (8.3%)	1 (8.3%)	
Normal sinus rhythm	48*	15 (31.2%)	13 (27.1%)	10 (21%)	9 (18.7%)	1 (2.1%)
Total	60*	18 (30%)	20 (33.3%)	11 (18.3%)	10 (16.6%)	1 (1.6%)

*One patient treated on 2 admissions.

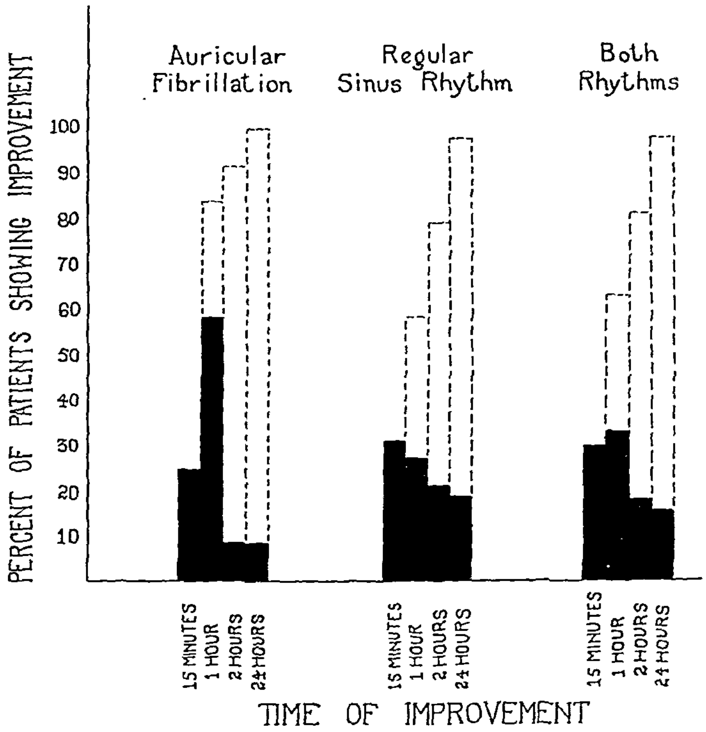

Fig. 3.—Time of onset of improvement in relation to type of cardiac mechanism.

The cardiac mechanism appeared to have some relationship to the time of onset of improvement (see Table III and Fig. 3). Eighty-three per cent of the patients with auricular fibrillation were improved within one hour, whereas only 58 per cent of those with normal sinus rhythm showed improvement in this period.

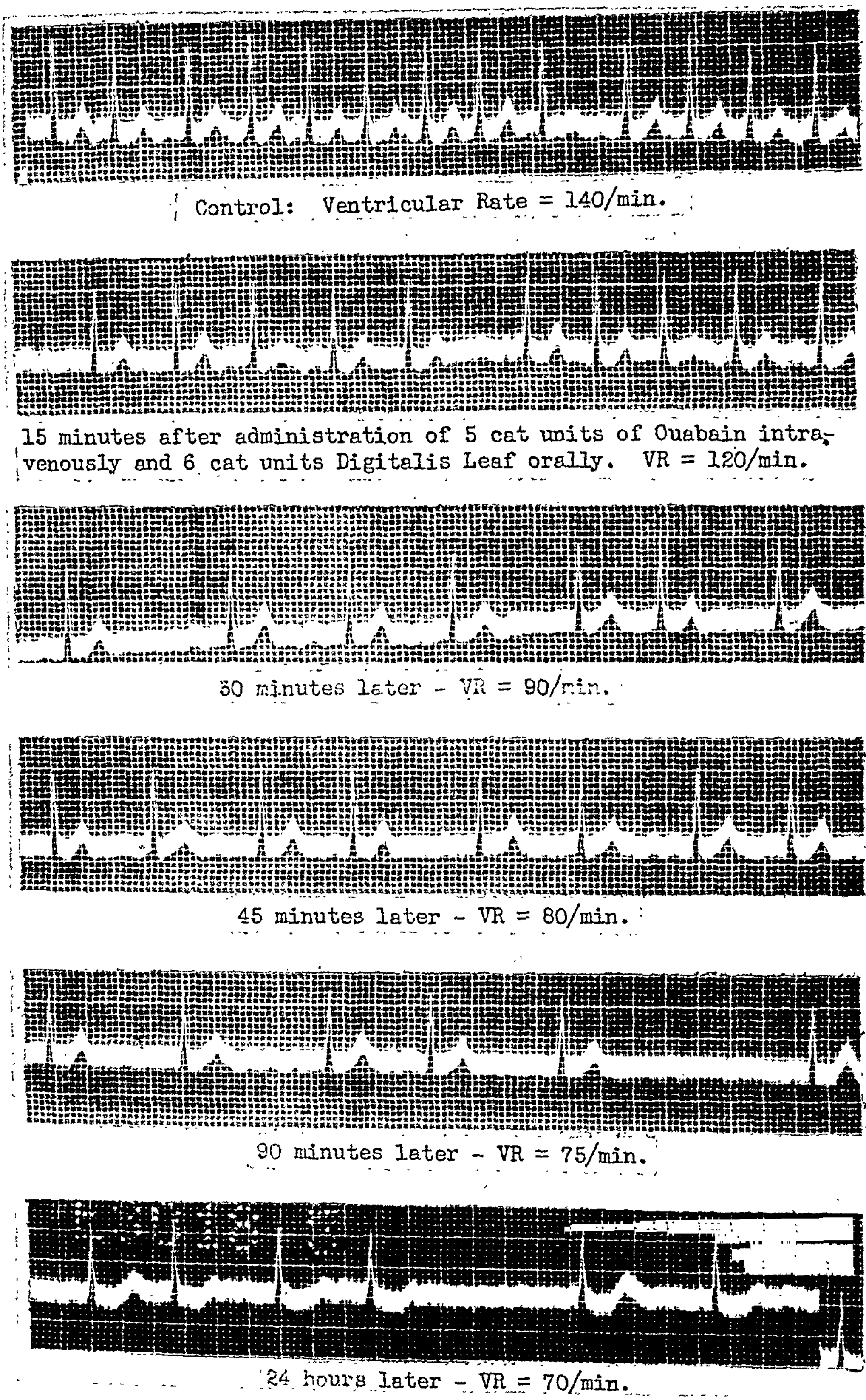

Fig. 4.—Electrocardiogram of a patient with auricular fibrillation, following digitalization by means of a combination of *oubain and digitalis leaf.*

There was no definite correlation between the degree of congestive heart failure and the time of onset of improvement. The age of the patient was not a factor.

A typical response to this method of digitalization is illustrated by the consecutive electrocardiograms of a patient with auricular fibrillation (see Fig. 4). Fifteen minutes after beginning treatment there was a significant reduction in the ventricular rate. Ventricular slowing continued progressively, and the full therapeutic response was achieved within twenty-four hours. This effect was maintained with two cat units of digitalis leaf daily. Fig. 5 illustrates the course of events in a patient with normal sinus rhythm. There was rapid improvement in the patient's appearance. His respiratory difficulty

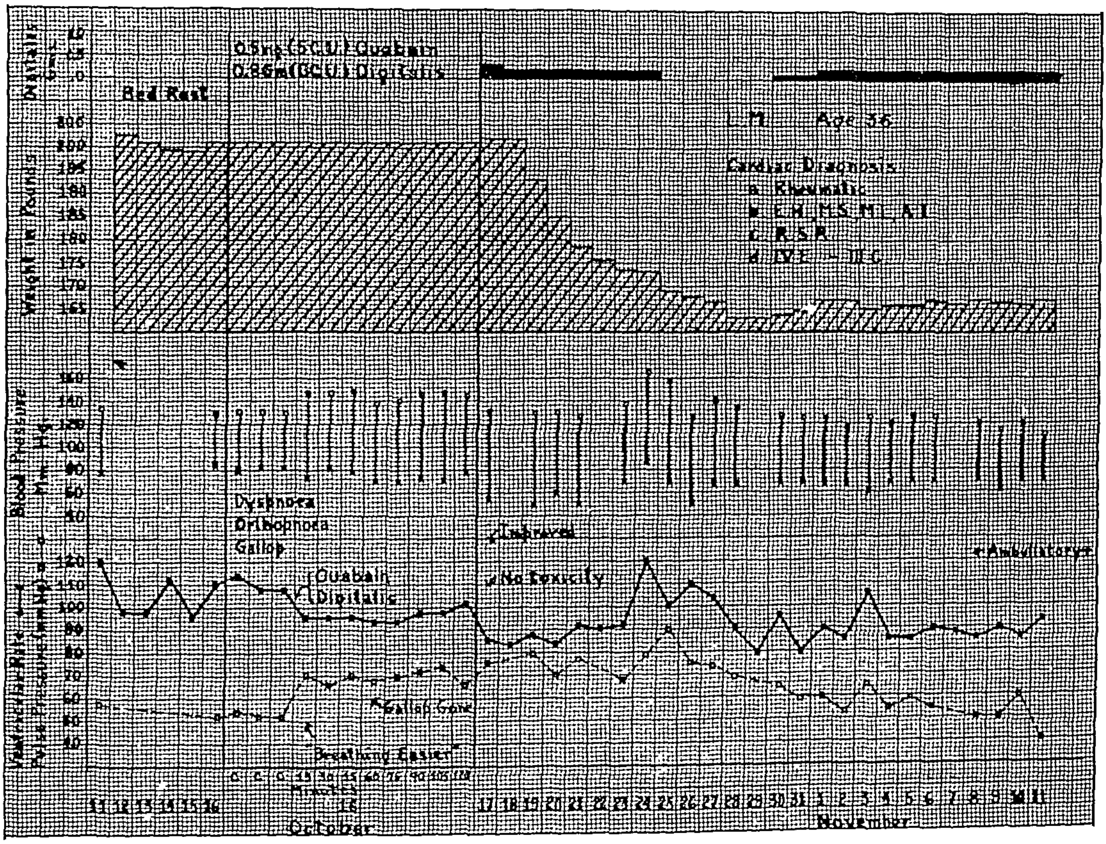

Fig. 5.—Clinical course of patient with normal sinus rhythm, following digitalization by means of a combination of ouabain and digitalis leaf. M. N., aged 42 years, had rheumatic heart disease, mitral stenosis and insufficiency. Weight was 107 pounds. Clinical improvement was shown within fifteen minutes. There was no digitalis toxicity.

decreased, and the pulse pressure rose from 51 to 70 mm. Hg. Within one hour his gallop rhythm disappeared. His condition improved progressively during the following twenty-four hours. A daily maintenance dose of digitalis leaf by mouth caused a rapid loss of edema, as evidenced by the weight curve. Anorexia and nausea occurred on the ninth day of digitalization. Digitalis therapy was discontinued for five days and then reinstituted, and the patient's course thereafter was uneventful.

TOXICITY

Eleven patients (18 per cent) showed evidences of mild toxicity at the end of twenty-four hours (Table IV); six had anorexia, seven, nausea, three, vomiting, and four, prolongation of the P-R interval of the electrocardiogram. Neither abnormal rhythms nor multiple premature systoles were observed. When symptoms of toxicity developed, there was an apparent relationship between the dose of digitalis leaf and the weight of the patient. Of the eight patients who became toxic on 6 cat units of digitalis, six weighed less than 120 pounds. Two of the three patients who received 8 cat units of digitalis leaf weighed less than 150 pounds. It is therefore recommended that, with this method of treatment, the dose of digitalis be regulated in the following manner: For patients who weigh less than 125 pounds, use 4 cat units (0.4 Gm.); for those who weigh between 125 and 175 pounds, 6 cat units (0.6 Gm.); and for those who weigh over 175 pounds, 8 cat units (0.8 Gm.).

COMMENT

The occurrence of mild toxicity in the above cases is indicative of complete digitalization. Evidence that a concentration of digitalis high in the therapeutic range was obtained is furnished by the appearance of mild toxicity in five other cases in which a maintenance dose of two cat units (0.2 Gm.) of digitalis leaf was given for from one to four days.

This method of therapy has the following advantages: (1) the use of ouabain brings about rapid improvement; (2) the simultaneous administration of the more slowly absorbed digitalis leaf not only maintains this improvement, but also decreases or abolishes the gap between the beginning of digitalization and the establishment of a maintenance dose; (3) although more rapid than the usual method of digitalization, this method is a safe one, and is no more likely to produce toxicity; (4) the method is applicable to patients with normal sinus rhythm, as well as those with auricular fibrillation; (5) the technique of administration is relatively easy. Complicated calculations are not necessary to estimate the initial and subsequent doses of digitalis.

SUMMARY

1. A method of obtaining rapid digitalization by the simultaneous administration of ouabain intravenously and digitalis leaf orally is presented.

2. Digitalization was produced sixty times in fifty-nine cases. The patients had varying degrees of congestive heart failure and different types of heart disease; their ages ranged from 28 to 79 years.

TABLE IV

PATIENTS PRESENTING EVIDENCE OF TOXICITY TWENTY-FOUR HOURS AFTER DIGITALIZATION WITH OUABAIN AND DIGITALIS LEAF

PATIENT	AGE	WT.	DIAGNOSIS	RHYTHM	DOSE OF DIG. LEAF	ANOREXIA	NAUSEA	VOMITING	EKG CHANGES
S.D.	28	140	Rheumatic. EH, MS, MI, AI.	AF	8		Y	Y	
M.S.	72	100	Arteriosclerotic. EH, CS, MF.	AF	6	Y	Y		
R.F.	48	105	Rheumatic and Hyper. EH, MI, MS.	RSR	6	Y	Y		P-R interval 0.21 sec.
R.S.	60	110	Hyper. and AS. EH, CS, MF.	RSR	6				P-R interval 0.33 sec.
A.R.	49	140	Rheumatic. EH, MS, MI, AI.	RSR	6	Y			
J.B.	57	107	Hyper. EH, Dil. Aorta.	RSR	6	Y	Y	Y	
D.H.	69	172	Hyper. and AS. EH, CS, MF.	RSR	8	Y	Y		
R.L.	48	150	Arteriosclerotic. EH, CS, MF, Old Myo. Infarct.	RSR	8	Y	Y		
R.P.	65	105	Hyper. and AS. EH, CS, MF.	RSR	6		Y	Y	
M.N.	73	117	Hyper. EH.	RSR	6				P-R interval 0.22 sec.
J.R.	71	145	Arteriosclerosis. EH, CS, MF. Recent Myo. Infarct.	RSR	6				P-R interval 0.24 sec.
TOTAL 11 patients (18.3%)						6	7	3	4

3. In the majority of the cases, improvement occurred within one hour. This improvement, once established, was progressive; the maximum effect was attained at the end of twenty-four hours.

4. After the initial digitalization, it was not difficult to establish the maintenance dose of digitalis leaf.

5. The method was found to be applicable to patients with normal sinus rhythm, as well as to those with auricular fibrillation.

6. Evidences of toxicity were the least that could be expected, indicating that the method is a safe one.

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RHEUMATIC HEART DISEASE

An Analysis of 796 Cases

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THE term "rheumatic heart disease" includes (1) the type of valvulitis and vegetation immediately associated with acute rheumatic fever or chorea, (2) valve deformities resulting from previous attacks of acute rheumatic valvulitis, and (3) the rather unusual condition of adherent pericardium without an associated valvular deformity, or cases in which, even if there is a slight valvular deformity, death results for the most part from the adherent pericardium. Rheumatic infection of the pericardium or myocardium, without valvulitis, is rarely seen.

The verrucous vegetations which are associated with acute rheumatic fever are so characteristic of rheumatic infection that a diagnosis of rheumatic valvulitis can be made without the immediate presence of rheumatic arthritis. These valvular lesions are probably the most common and most characteristic manifestations of rheumatic infection. A few of the cases reported herein as instances of acute or recurrent rheumatic endocarditis are included for anatomic reasons.

Nonsyphilitic valvular deformities resulting in stenosis and insufficiency are caused by previous attacks of rheumatic valvulitis. Proliferative inflammation occurs in the valve. This results in a scar which commonly becomes calcified. Although bacterial valvulitis may bring about an increase in the amount of connective tissue in a valve, healing in clinically typical cases of bacterial endocarditis is so rare that it becomes obvious that healed valve deformities, which are so commonly responsible for cardiac failure in the middle and later decades, are seldom, if ever, the result of bacterial endocarditis.

Atherosclerosis is commonly found in the valves, especially the mitral, but available evidence seems to indicate that atherosclerotic changes in the cusps, although common, are seldom, if ever, severe enough to produce valvular stenosis or insufficiency of a degree sufficient to cause cardiac failure.

If we exclude tuberculous pericarditis, the cardiac failure which is caused by an adherent pericardium appears, in most cases, to be the result of a rheumatic infection. This condition seldom occurs except in association with a rheumatic valvular involvement.

In this paper, the autopsy cases of rheumatic heart disease which were encountered in the Department of Pathology at the University

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of Minnesota during the years 1910-1937 are analyzed in respect to general incidence, incidence of types, etiology, pathology, and pathogenesis; and some important clinical applications are derived from the analysis.

General Incidence.—During the years 1910-1937 there were 27,957 autopsies, of which 4,254 were done on patients with noncongenital cardiac disease (15.2 per cent). In 1,598 (37.6 per cent) of these cases, the disease was infectious in origin (rheumatic; bacterial; syphilitic; toxic myocarditis). There were 796 cases of rheumatic heart disease (Table I). This comprised about 50 per cent of all of the cases of infectious heart disease, and 18.7 per cent of the total number of cases of noncongenital cardiac disease.

TABLE I

TYPES OF RHEUMATIC HEART DISEASE (796 CASES)

1. Acute rheumatic endocarditis (98)		12.31%
2. Recurrent rheumatic endocarditis (76)		9.54
3. Valve deformities (586)		73.61
a. Incompletely healed (113)	19.28%	
b. Completely healed (239)	40.78	
c. Calcified, nodular, aortic (234)	39.93	
4. Adherent pericardium (36)		4.52

Incidence of Types.—The cases of rheumatic heart disease (Table I) were divided into four groups: acute rheumatic endocarditis, ninety-eight cases (12.31 per cent); recurrent rheumatic endocarditis, seventy-six cases (9.54 per cent); valve deformities, 586 cases (73.6 per cent), and adherent pericardium, thirty-six cases (4.52 per cent). The first was characterized by the fact that there were verrucous vegetations on valves which, by gross examination, appeared not to have been previously thickened. Upon microscopic examination, however, some of the valves in this group were found to have such well-developed blood vessels that the possibility of a previous infection was suggested. The dividing line between acute rheumatic and recurrent rheumatic endocarditis is not sharp.

The second group, comprising cases of recurrent rheumatic endocarditis, was similar to the first, except that the vegetations were on grossly thickened fibrous valves. In many cases there was a history of repeated attacks of rheumatic fever.

In the third group, made up of cases of healed valve deformities, there were thickened, scarred, and, frequently, calcified valves. In some instances, evidences of lack of complete healing could be detected, especially microscopically.

This third group of cases of rheumatic heart disease was further divided into three subgroups: (a) incompletely healed valves, 113 cases (19.28 per cent); (b) completely healed valves, 239 cases (40.78 per cent); and (c) calcified, nodular aortic valves, 234 cases (39.93

per cent). The last subgroup was studied separately, for it is thought by some that this lesion results from a metabolic disturbance or atherosclerosis, rather than rheumatic infection, and because it is a fairly definite clinical entity. A study of this type of valve deformity has already been reported.[1] Evidence definitely favors the theory of rheumatic origin of this lesion. There appears to be no more evidence that the aortic valvular deformity, with calcification, is nonrheumatic in origin than that the calcific mitral valvular deformity is not the result of rheumatic infection. Calcification of the scarred valve is as common in the mitral valve as in the aortic. In fact, there are few extensively scarred valves which are not calcified to a greater or less degree. If all of the calcific aortic valvular deformities were regarded as nonrheumatic in origin, it would have to be concluded that the aortic valve is not commonly attacked by the rheumatic infectious agent. At least 85 per cent of deformed aortic valves are calcified.

The fourth group, comprising cases of rheumatic heart disease in which death appeared to have been caused primarily by an adherent pericardium, was small (thirty-six cases, or 4.52 per cent). In more than half of these, slight valvular deformities were present also. In only fifteen of the thirty-six cases were the valves normal grossly. Death purely as a result of adherent pericardium is rare.

Etiology.—The etiology of acute rheumatic fever and rheumatic heart disease is considered in this paper in detail only in so far as information can be obtained from those cases in which an autopsy was performed. Age and sex are discussed as etiologic factors.

It is generally believed that acute rheumatic fever is an infectious disease. There is no general agreement concerning the nature of the infectious agent. The three theories are (1) that it is caused by an unknown infectious agent; (2) that it is caused by the *Streptococcus hemolyticus* or *viridans;* and (3) that it is a virus infection. The first theory is based primarily on the belief that the rheumatic inflammation is of a specific type. The material which forms the basis of this report furnishes some information on this point, and this will be considered further under the discussion of rheumatic inflammation. The *Streptococcus viridans* is the organism which has been most commonly isolated from the blood, joints, and pericardial exudates of patients with acute rheumatic fever. This occurred in many of the cases of acute and recurrent rheumatic endocarditis in this series. These streptococci are regarded by some as secondary invaders, but the relatively high percentage of positive cultures from previously healthy persons who became ill rather suddenly with acute rheumatic fever does not strongly support this. Streptococcic allergy is generally considered, by those who believe in the streptococcic theory, to be a conspicuous factor in the pathogenesis of rheumatic inflammation. The virus theory is based primarily upon the observations of Schlesinger, et al.[2] They found

bodies in the pericardial exudate which resembled the elementary bodies of a virus. Recently, Sabin[3] has isolated filtrable pleuropneumonia-like organisms from mice. These organisms, when injected into other mice, were capable of producing arthritis in a high percentage of cases. Swift[4] has isolated a similar organism from rheumatic patients. There is nothing about the type of inflammation in rheumatic heart disease which definitely favors or disfavors the theory that a virus is the active agent in rheumatic infection. The type of cellular reaction which occurs in rheumatic inflammation can be simulated closely experimentally by injecting rabbits, especially those which are allergic, with streptococci.

The age and sex incidence in the cases of acute rheumatic endocarditis is shown in Table II. Death occurred early in this group; 71.4 per

TABLE II

AGE AND SEX INCIDENCE OF ACUTE AND RECURRENT RHEUMATIC ENDOCARDITIS (174 CASES)

DECADE	ACUTE RHEUMATIC (98 CASES)						RECURRENT RHEUMATIC (76 CASES)					
	MALES 49		FEMALES 49		TOTAL		MALES 38		FEMALES 38		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	15	30.6	16	32.6	31	31.6	0	0	3	7.9	3	3.9
2	17	34.7	15	30.6	32	32.6	7	18.4	12	31.6	19	25.0
3	3	6.1	9	18.4	12	12.2	7	18.4	5	13.2	12	15.8
4	4	8.2	4	8.2	8	8.2	9	23.7	4	10.5	13	17.1
5	2	4.1	1	2.0	3	3.1	6	15.8	9	23.7	15	19.7
6	3	6.1	0	0	3	3.1	6	15.8	4	10.5	10	13.2
7	3	6.1	1	2.0	4	4.1	2	5.2	0	0	2	2.6
8	1	2.0	0	0	1	1.0	1	2.6	1	2.6	2	2.6
9	1	2.0	2	4.1	3	3.1	0	0	0	0	0	0
10	0	0	1	2.0	1	1.0	0	0	0	0	0	0
Total	49	99.9	49	99.9	98	100.0	38	99.9	38	100.0	76	99.9

cent of the males and 81.6 per cent of the females, or a total of 76.4 per cent, died in the first three decades. There were forty-nine males and forty-nine females.

Of the seventy-six patients who had recurrent rheumatic endocarditis (Table II), the greatest percentage of males (23.7 per cent) died in the fourth decade, and the greatest percentage of females (31.6 per cent) in the second decade; 90.8 per cent of the total number died in the second to sixth decades, inclusive. Death occurred at a later stage than in the acute rheumatic group. The number of males and females was the same, thirty-eight each. It is probable that more females than males died with recurrent rheumatic endocarditis, for in the later decades the number of males in our series is about twice the number of females.

The age and sex incidence of the valve deformities in subgroups "a" and "b," of group III, is shown in Table III. There were 352 cases, 179 in males and 173 in females. By correcting for the fact that twice as many males as females come to autopsy in most of the decades of this group, there would be nearly twice as many females in these two

groups. This greater number of females is probably accounted for by the fact that patients with aortic lesions were taken from these groups and placed in subgroup "c."

The highest death rate for both sexes in subgroups "a" and "b" occurred in the fifth decade; 90.6 per cent of the total number in the two groups died between the third and seventh decades, inclusive. Death from these valve deformities occurred, as a rule, later in life than among the patients with acute or recurrent rheumatic infection.

In subgroup "c" (calcified, nodular, aortic valvular deformity) there was a decided preponderance of males (males 197 and females 37) (Table III). Death occurred later in subgroup "c" than in subgroups "a" and "b." The greatest percentage of patients of both sexes in subgroup "c" died in the sixth decade; 90.2 per cent of the total number died between the fourth and eighth decades. The reason for the greater average length of life in this group is the fact that the chief lesion was of the aortic valve, for, as was shown in a previous publication,[5] a patient with an aortic lesion will live, on an average, from fifteen to twenty years longer than one with a mitral deformity.

TABLE III

AGE AND SEX INCIDENCE IN CASES OF VALVULAR DEFORMITIES (586 CASES)

DECADE	SUBGROUPS "A" AND "B" (352)						SUBGROUP "C" (234)					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	1	0.6	3	1.7	4	1.1	0	0	0	0	0	0
2	2	1.1	4	2.3	6	1.7	2	1.0	1	2.7	3	1.3
3	22	12.3	19	11.0	41	11.7	7	3.6	3	8.1	10	4.3
4	38	21.2	35	20.2	73	20.8	24	12.1	3	8.1	27	11.5
5	62	34.6	45	26.0	107	30.3	35	17.8	5	13.5	40	17.1
6	32	17.9	35	20.2	67	19.0	46	23.4	9	24.3	55	23.6
7	11	6.1	20	11.6	31	8.8	43	21.8	5	13.5	48	20.5
8	8	4.5	10	5.8	18	5.1	36	18.2	5	13.5	41	17.5
9	3	1.7	2	1.2	5	1.4	4	2.0	5	13.5	9	3.8
10	0	0	0	0	0	0	0	0	1	2.7	1	0.4
Total	179	100.0	173	100.0	352	99.9	197	99.9	37	99.9	234	100.0

Of the thirty-six patients who died from the effects of an adherent pericardium, twenty-seven were males and nine were females. The death rate was highest among the males in the second and third decades, and, among the females, in the second, fourth, and fifth decades.

There were 490 males and 306 females in this series of 796 cases of rheumatic heart disease. This does not approximate the relative sex incidence of rheumatic heart disease in the general population, for, from the third decade upward, there were twice as many males as females in the autopsy material.

To obtain, approximately, the relative incidence of rheumatic heart disease in males and females, the number of male or female patients who had any of the types of rheumatic heart disease was compared with the total number of males or females who came to autopsy (Table

IV). There were 18,227 autopsies on males, and 9,730 on females. This gave a percentage, in males, of 2.688, and, in females, of 3.144 of patients with rheumatic heart disease. When expressed as the number of cases of rheumatic heart disease per thousand autopsies, there were about twenty-seven males, and thirty-one females, respectively, per thousand.

It cannot be said definitely that this sex ratio holds in the general population, for there may be some degree of selection of cases in an autopsy service; however, the autopsy material at the University of Minnesota is *fairly well distributed*. It comes from several public and private hospitals, from the coroner's service, and from physicians in private practice. Furthermore, the percentage of autopsies obtained in most of the hospitals is high. In the city of Minneapolis it is about 15 per cent. It seems fair to conclude that rheumatic heart disease occurs with about the same frequency in the two sexes.

Pathology and Pathogenesis.—The pathologic changes in the valves and endocardium, the myocardium, the coronary arteries, and the pericardium were studied.

The valves which are involved in rheumatic heart disease are primarily the aortic and mitral, but the tricuspid and pulmonic valves are not infrequently infected, especially when the disease is acute, and generally in association with involvement of the aortic or mitral valves, or both. In the ninety-eight cases of acute rheumatic endocarditis (Table V),

TABLE IV

SEX INCIDENCE OF THE DIFFERENT KINDS OF RHEUMATIC HEART DISEASE IN THE ENTIRE AUTOPSY SERIES (18,227 MALES AND 9,730 FEMALES)

	MALES			FEMALES		
	NO. AUTOPSIES	NO.	%	NO. AUTOPSIES	NO.	%
Acute rheumatic	18,227	49	0.268	9,730	49	0.503
Recurrent rheumatic	18,227	38	0.208	9,730	38	0.390
Valve deformity Subgroups "a" and "b"	18,227	179	0.982	9,730	173	1.778
Valve deformity Subgroup "c"	18,227	197	1.080	9,730	37	0.380
Adherent pericardium	18,227	27	0.148	9,730	9	0.092
Total	18,227	490	2.688	9,730	306	3.144

the aortic valve was involved alone twice, the mitral valve alone forty-three times, both the aortic and mitral twenty-four times, the tricuspid and mitral nine times, and the tricuspid, aortic, and mitral ten times; there were no cases of involvement of the tricuspid alone, of the tricuspid and aortic, or of the tricuspid and pulmonic. The tricuspid valve was affected, in all, twenty-eight times. The pulmonic valve was involved but once, and, in this case, it was the only valve affected.

Of the seventy-six cases of recurrent rheumatic endocarditis (Table V), the aortic valve alone was infected in but two cases, the mitral

TABLE V

COMBINATIONS OF VALVE INVOLVEMENT IN RHEUMATIC HEART DISEASE (780 CASES)

	A	M	T	P	AM	AT	AP	AMT	AMP	AMTP	MT	MTP	TP	TOTAL
Acute rheumatic	2	43	0	1	24	0	0	10	0	9	9	0	0	98
Recurrent rheumatic	2	21	0	0	30	1	0	11	1	4	6	0	0	76
Valve deformities														
Subgroup "a"	4	65	0	0	28	0	0	8	0	1	7	0	0	113
Subgroup "b"	17	149	0	1	45	0	0	17	0	0	9	0	0	238
Subgroup "c"	136	0	0	0	92	1	0	5	0	0	0	0	0	234
Adherent pericardium	6	11	0	0	2	0	0	1	0	0	0	0	0	20
Total	167	289	0	2	221	2	0	52	1	14	31	0	0	779

valve alone in twenty-one, and the aortic and mitral, together, in thirty. Involvement of the tricuspid alone did not occur. Tricuspid and aortic involvement was noted once, tricuspid and mitral six times, tricuspid, aortic, and mitral eleven times, and tricuspid, pulmonic, aortic, and mitral, four times. In all, the tricuspid was involved twenty-two times, always in combination with involvement of one or more of the other valves. The pulmonic valve was affected four times only, and always in combination with involvement of the aortic, mitral, and tricuspid valves.

Of the 113 cases of subgroup "a" of the valve deformities (Table V), the aortic valve was deformed alone in four, the mitral valve alone in sixty-five, and the aortic and mitral, together, in twenty-eight.

In the 239 cases of subgroup "b" of the valve deformities (Table V), involvement of the aortic valve alone was noted seventeen times, of the mitral alone 149 times, and of the aortic and mitral, together, forty-five times. In the third subgroup of healed valve deformities, comprising calcified, nodular, aortic lesions (234 cases), there was naturally a high incidence of involvement of the aortic valve, for it was upon the character of this valve deformity that this classification was made. The aortic valve alone showed deformity in 136 cases, and both the aortic and mitral in ninety-seven (Table V).

It is possible, and even probable, that the tricuspid and pulmonic valves may have been infected and slightly thickened in any of the cases of valve deformity, but the degree was not marked. A slight degree of valvular deformity cannot be recognized as easily by gross examination as the verrucous vegetations in the cases of acute and recurrent rheumatic endocarditis.

The valves of the left side of the heart showed the greatest incidence of involvement (Table V). Of the 780 cases of rheumatic heart disease in which the valves were affected, there was involvement of the aortic, mitral, or both, in 779 (99.8 per cent). In forty-four (5.6 per cent), the valves on the right side of the heart were affected, and, in all of these except one (pulmonic alone), there was an associated aortic or mitral involvement.

The relation of sex to the three kinds of valvular involvement (aortic alone, mitral alone, and both aortic and mitral) is apparently significant, and may offer an explanation for the high incidence of the calcified, nodular, aortic valvular deformity (subgroup "c") in men who die, as a rule, in the later decades.

In discussing varieties of valvular involvement, three terms are used, namely, aortic alone, mitral alone, and aortic and mitral combined. Any of these may be associated with tricuspid or pulmonic disease. The term "aortic alone" is used to mean that there is no mitral involvement, and "mitral alone" that there is no associated aortic lesion.

TABLE VI

PERCENTAGE OF CASES IN WHICH DEATH WAS CAUSED BY RHEUMATIC HEART DISEASE OR BACTERIAL ENDOCARDITIS, WITH THE FOLLOWING VALVULAR INVOLVEMENT: AORTIC, MITRAL, AORTIC AND MITRAL COMBINED (778 RHEUMATIC CASES AND 455 CASES OF BACTERIAL ENDOCARDITIS; TOTAL 1,233 CASES)

MALES, 18,227 AUTOPSIES	A		M		AM		TOTAL	
Acute and recurrent rheumatic	5	0.027	38	0.208	43	0.235	86	0.471
Valve deformity, "a" and "b," and adherent pericardium	21	0.115	110	0.603	64	0.351	195	1.069
Valve deformity "c"	122	0.669	0	0	75	0.410	197	1.080
Total rheumatic, 778; males, 478; females, 300	148	0.811	148	0.811	182	0.998	478	2.622
Bacterial, 455; males, 282; females, 173	75	0.411	103	0.565	104	0.570	282	1.547
Total valvular, 1,233	223	1.223	251	1.377	292	1.602	760	4.169

FEMALES, 9,730 AUTOPSIES	A		M		AM		TOTAL	
Acute and recurrent rheumatic	0	0	50	0.513	37	0.380	87	0.894
Valve deformity, "a" and "b," and adherent pericardium	7	0.071	132	1.356	37	0.380	176	1.808
Valve deformity "c"	15	0.154	0	0	22	0.226	37	0.380
Total rheumatic, 778; males, 478; females, 300	22	0.226	182	1.870	96	0.986	300	3.083
Bacterial, 455; males, 282; females, 173	25	0.256	105	1.079	43	0.441	173	1.778
Total valvular, 1,233	47	0.483	287	2.949	139	1.428	473	4.861

There were 478 males and 300 females in the series of 778 cases of rheumatic heart disease in which one of the forms of valvular involvement (aortic alone, mitral alone, or aortic and mitral combined) was present. In Table VI they are placed in three groups: (1) cases of acute and recurrent rheumatic endocarditis; (2) cases of incompletely and completely healed valvular deformities, and cases of adherent pericardium with a valvular deformity, also; and (3) cases in which there was a calcified, nodular, aortic lesion. It is important to note that the percentage of deaths caused by aortic valvular involvement alone was greater, and increased more rapidly, from group 1 to group 3 among the males than among the females. Group 3 included older persons. The mitral alone among the females showed about the same proportional increase, except that there was no mitral alone involvement. The total percentages of combined aortic and mitral involvement were about the same in the two sexes. Among the males the percentage increased from 0.235 in the first group to 0.410 in the third. Among the females the percentage was 0.380 in each of the first 2 groups, but less (0.226) in the third group. As shown in the total rheumatic column, the percentages of aortic alone, mitral alone, and aortic and mitral combined among the males, and aortic and mitral combined among the females, were approximately the same (0.811, 0.811, 0.998, and 0.986, respectively). The incidence of aortic and mitral involvement

among the males was the same. Mitral involvement among the females was 8.274 times as common as aortic. The outstanding differences in percentages were in the incidence of aortic alone and mitral alone among the females. The aortic alone was less, and the mitral alone was greater among the females than the males. It is obvious that females are much more likely to have infection in the mitral valve than in the aortic. This selective valvular involvement was also noted in the 455 cases of bacterial endocarditis (Table VI). The reason for it is not understood.

The gross appearance of the diseased valves presented several interesting features. In acute and recurrent rheumatic valvulitis the vegetations were always on the ventricular surfaces, a short distance from the free margins, of the aortic and pulmonic cusps, and on the auricular surfaces, also a short distance from the free margins, of the mitral and tricuspid cusps. The fact that these surfaces of the valves contain the spongiosa layer, and that there are more vessels in this layer than in the fibrosa on the opposite side of the cusps supports the embolic theory of the pathogenesis of acute rheumatic endocarditis.

The thickening and scarring of the valves, as was shown in a previous paper, are caused by cellular proliferation, which results in an increase of connective tissue within the valve. There is no organization of a thrombus. In rheumatic valvulitis very little thrombus is formed, and what there is contains little or no fibrin. The chordae tendineae are also involved, with resultant thickening and shortening. The scars in all of the valves show a great tendency to undergo calcification, and it is not uncommon to find areas of ossification.

That normal valves have vessels is affirmed by some[6] and denied by others.[7] Those who deny that they exist believe that when vessels are present the valve has previously been inflamed, and that this inflammation has resulted in the development of vessels. The evidence obtained by injecting the coronary arteries and by microscopic examination of the valves seems to favor the belief that normal valves have small vessels which rapidly become congested and enlarged during inflammation.

Microscopically, vessels are easily seen in the inflamed valves early in the course of acute rheumatic valvulitis and acute bacterial endocarditis. These vessels may or may not extend from the point of the vegetation to the ring. Some of the vessels may be seen communicating with indentations on the free surface of the valve, which suggests that they may open through the endothelium of the valve; this occurs in the heart, and, as Winternitz, et al.,[8] have shown, also in the arteries. It seems evident from the association of an increase in vessels and proliferative and exudative inflammation in the ring that, in most cases, the infectious agent probably enters the valve, by way of the coronary vessels, through the ring, but, in not a few instances, an early inflam-

mation, with increased formation of vessels, is seen near the distal part of the cusp, without any evidence of involvement of the proximal part of the valve and the ring. This suggests the possibility that a valve may become infected directly from the blood stream. More work will have to be done before the pathogenesis of acute rheumatic valvulitis can be fully understood.

Microscopically, the inflammation is primarily proliferative. There are large cells with dark-staining nuclei. Others have large, vesicular nuclei. Some of the cells are multinucleated. They resemble the cells which are found in the Aschoff nodules in the myocardium and in rheumatic subcutaneous nodules. A hyaline substance, designated as fibrinoid material by Klinge,[9] and degenerated collagen by Gross and Ehrlich,[10] is also noted. This appears early in the course of the reaction. The inflammation is generally confined to the valves, but the endothelium may break and a platelet thrombus form; this thrombus bears a close resemblance to that which occurs in bacterial endocarditis, except that the latter is larger and contains bacterial colonies.

When the inflammation subsides the nuclei become smaller and a scar remains. Recurrences are common. The end result is a healed deformity of the valve. Evidences of previous inflammation are as common in the calcified, nodular, aortic type as in other forms of healed valvular deformities. The processes which lead to scarring of the mitral and aortic valves appear to be similar.

The *endocardium* of the auricles, as was pointed out by MacCallum,[11] and later confirmed by our observations, is affected in acute rheumatic endocarditis with about the same frequency (40 per cent) as in subacute bacterial endocarditis. There were no rheumatic vegetations on the ventricular endocardium, except on the chordae tendineae, in our cases of acute rheumatic endocarditis.

The chief gross change noted in the *myocardium* was hypertrophy, and the criterion of hypertrophy was an increase in the weight of the heart. This increase in weight was common in cases of acute and recurrent rheumatic endocarditis, but the degree of increase was not ascertained as accurately as in the cases of healed valve deformity, for there was a greater variation in age, and the presence of fibrinous pericarditis made it difficult to obtain the exact weight of the myocardium. The cause of the hypertrophy seems to have been valvular insufficiency.

When the heart weighed 500 grams, or more, in males, and 450 grams, or more, in females, it was regarded as definitely hypertrophied. A weight of 400 to 499 grams, in males, and 350 to 449 grams, in females, was taken to indicate that hypertrophy was probably present, especially in the upper brackets. Weights below 400 grams, in males, and 350 grams, in females, were considered normal; if any of these hearts came from small persons, they may have been slightly hypertrophied. The

foregoing estimates, although they do not take into account the relation of body weight to heart weight in each individual case, agree well with the observations of Smith,[12] in his comparison of body weights and heart weights. His maximum, average, normal heart weight for a male weighing 200 pounds was 412 grams, and, for a woman weighing 195 pounds, 371 grams. The possibilities of error in our estimations of hypertrophy are obviously on the side of passing slightly hypertrophied hearts as normal. This was not regarded as serious in our series, for, inasmuch as many different pathologists performed the autopsies, there was bound to be a variation in the amount of aorta left attached to the heart. Many of the hearts were weighed on spring balances, which might introduce another error.

The heart weights in 339 of the 352 cases in subgroups "a" and "b," of group III (healed and unhealed valve deformities), are shown

TABLE VII

DEGREE OF HYPERTROPHY IN CASES OF RHEUMATIC VALVE DEFORMITIES AND ADHERENT PERICARDIUM

CODE OF WEIGHTS OF HEARTS
1. MALES BELOW 400 GRAMS, FEMALES BELOW 350 GRAMS
2. MALES 400-499, FEMALES 350-449
3. MALES 500-799, FEMALES 450-749
4. MALES 800 OR MORE, FEMALES 750 OR MORE

	VALVE DEFORMITIES SUBGROUPS "A" AND "B" (339)						VALVE DEFORMITIES SUBGROUP "C" (234)					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	24	14.1	26	15.4	50	14.7	4	2.0	2	5.4	6	2.6
2	34	20.0	66	39.0	100	29.5	27	13.7	11	29.7	38	16.2
3	102	60.0	75	44.4	177	52.2	135	68.5	24	64.9	159	68.0
4	10	5.8	2	1.2	12	3.5	31	15.7	0	0	31	13.2
	170	99.9	169	100.0	339	99.9	197	99.9	37	100.0	234	100.0
	ADHERENT PERICARDIUM (26)						TOTAL 599					
	MALES		FEMALES		TOTAL		MALES		FEMALES		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
1	3	15.0	0	0	3	11.5	31		28		59	9.8
2	2	10.0	2	33.3	4	15.4	63		79		142	23.7
3	5	25.0	2	33.3	7	26.9	242		101		343	57.3
4	10	50.0	2	33.3	12	46.1	51		4		55	9.2
	20	100.0	6	99.9	26	99.9	387		212		599	100.0

in Table VII. The weights were not recorded in all of the 352 cases In twenty-four males (14.1 per cent) and twenty-six females (15.4 per cent), a total of fifty (14.7 per cent), the hearts were not hypertrophied. Fifteen of the twenty-four males and twenty-one of the twenty-six females had mitral lesions only. In the group with doubtful hypertrophy there were thirty-four males (20 per cent) and sixty-six females (39 per cent), a total of 100 (29.5 per cent). Unquestionable, but not extensive, hypertrophy was present in 102 (60 per cent) of the males and seventy-five (44.4 per cent) of the females, a total of

177 (52.2 per cent). In all but fifty (14.7 per cent) of these 339 cases of valve deformities there was some degree of cardiac hypertrophy. The hearts of only ten males and two females (3.5 per cent) showed extensive hypertrophy (800 grams, or more, in males, and 750 grams, or more, in females). Of the 339 cases, there were mitral lesions in all but twenty; there were aortic lesions in 120, and, in twenty, aortic lesions only. Fifteen of the twenty-four males with heart weights below 400 grams, and twenty-one of the twenty-six females with heart weights below 350 grams, had mitral lesions only. With a preponderance of mitral deformities, especially when the deformity is stenosis, excessive hypertrophy is not common.

Hypertrophy was more common in the cases of calcified, nodular, aortic deformity (Table VII). There were 234 cases. Only four males (2 per cent) and two females (5.4 per cent), a total of six (2.6 per cent), had no hypertrophy. Cases of doubtful hypertrophy were also fewer than in the other groups of valve deformities; there were twenty-seven males (13.7 per cent), and eleven females (27.7 per cent), a total of thirty-eight (16.2 per cent). The percentage of females with doubtful hypertrophy, or none at all, was greater than that of the males. The number with definite, but not extensive, hypertrophy was high in this group; there were 135 males (68.5 per cent) and twenty-four females (64.9 per cent), a total of 159 (68 per cent). Excessive hypertrophy was also more common in this group. Thirty-one males (15.7 per cent) had hearts weighing 800 grams, or more. None of the females had excessive hypertrophy, amounting to 750 grams, or more. All members of this group had aortic valve deformities, and ninety-seven had a mitral deformity, also. Twenty-two of the ninety-seven with a mitral deformity were females.

The degree of cardiac hypertrophy in cases in which cardiac failure had been caused entirely or primarily by an adherent pericardium is shown in Table VII. Of the thirty-six cases, only twenty-six were considered. In some of the remaining ten cases the patient had been too young, or the weight of the heart was not recorded. There were twenty males and six females. Three of the males had hearts weighing less than 400 grams. None of the female hearts weighed less than 350 grams. Two males had hearts which weighed between 450 and 499 grams. Two female hearts weighed between 350 and 449 grams. Fifteen males had hearts weighing 500 grams, or more; ten weighed 800 grams, or more; the heaviest weighed 1,350 grams. Of course, in all of these cases a small part of the weight was contributed by the adherent pericardium. Four female hearts weighed from 450 grams to 750 grams; the heaviest weighed 750 grams.

Of the total of 599 hearts, only fifty-nine (9.8 per cent) failed to show some degree of hypertrophy. Cardiac hypertrophy is a common pathologic change in rheumatic heart disease, especially in cases in

which death results from healed valve deformities. The hypertrophy appears to be caused by increased work. The greatest degree of hypertrophy was found in the hearts which were the seat of an aortic valvular deformity, and when an adherent pericardium had been the chief cause of death.

Gross areas of fibrosis in the myocardium were seen only occasionally, and then with difficulty.

Microscopic examination of the myocardium revealed Aschoff nodules; diffuse inflammation, with a cellular reaction similar to that in the Aschoff nodules; abscesses; and periarterial scars which were partly or completely healed. A diffuse suppurative myocarditis was seldom observed.

The incidence of the different kinds of inflammation of the myocardium was ascertained by examining five sections from each heart. Sections of moderate size were taken from the apex and two other areas of the left ventricle, from the septum, and from the base of the right ventricle. Sometimes more sections were examined. Table VIII

TABLE VIII

EVIDENCE OF MYOCARDITIS IN RHEUMATIC HEART DISEASE (295)

	ASCHOFF NODULES		DIFFUSE INFLAMMATION		ABSCESSES		PERIARTERIAL SCARS		ONE OR MORE	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Acute rheumatic (67)	45	67.16	12	17.91	2	2.98	21	31.34	53	79.10
Recurrent rheumatic (53)	30	56.60	3	5.66	0	0	30	56.60	40	75.47
Valve deformity subgroup "a" (43)	7	16.27	3	6.97	0	0	24	55.81	25	58.13
Valve deformity subgroup "b" (65)	9	13.84	8	12.30	1	1.53	24	36.92	25	38.46
Valve deformity subgroup "c" (67)	7	10.44	4	5.97	0	0	32	47.76	33	49.25

gives the frequency of the various microscopic pathologic changes which were noted in the myocardium in 295 cases of rheumatic heart disease. There were sixty-seven cases of acute rheumatic endocarditis, fifty-three of recurrent rheumatic endocarditis, forty-three of incompletely healed valvular deformities, sixty-five of completely healed valvular deformities, and sixty-seven of calcified, nodular, aortic valve deformity.

The incidence of Aschoff nodules decreased from 67.1 per cent in the acute rheumatic group to 10.4 per cent in the calcified, nodular, aortic group. It was interesting to note that, as the activity of the inflammation decreased, the number of Aschoff nodules diminished, and that the incidence of Aschoff nodules in the two groups of completely healed valvular deformities was nearly the same.

A diffuse, proliferative inflammation was also most common in the acute rheumatic group, but did not decrease as regularly as the Aschoff nodules.

Abscesses were rare. They were seen in only two cases (2.98 per cent) in the acute rheumatic group, and in one (1.53 per cent) of the cases of completely healed valvular deformity.

The periarterial scars differ from those which occur in cases of coronary sclerosis. The former are immediately around the blood vessels, and may be seen in various stages, from degenerating Aschoff nodules and irregular proliferative inflammation, to a completely healed scar. The scar caused by coronary sclerosis is seldom near the vessel.

Periarterial scars were least common in the acute rheumatic group (31.3 per cent), and most numerous in the recurrent rheumatic group (56.6 per cent), but the incidence in the healed rheumatic groups was almost as great. The total incidence of one or more of the above microscopic changes was greatest in the acute rheumatic group (79.1 per cent). It was practically as large in the recurrent rheumatic group (75.4 per cent). In subgroups "a" and "b," of the valve deformities, it was 46.3 per cent, and, in subgroup "c," 49.2 per cent. This was significant in considering the etiology of the three groups of valvular deformities.

Another gross pathologic condition which was noted in rheumatic heart disease was pericarditis. Clinically, the occurrence of pericarditis is often used to help differentiate acute rheumatic endocarditis from bacterial endocarditis.

TABLE IX

INCIDENCE OF PERICARDITIS IN RHEUMATIC HEART DISEASE AND IN BACTERIAL ENDOCARDITIS

I. Rheumatic	
1. Acute rheumatic endocarditis	52.5
2. Recurrent rheumatic endocarditis	41.1
3. Valve deformities	17.0
Subgroup "a"	12.5
Subgroup "b"	22.2
Subgroup "c"	14.1
4. Adherent pericardium	100.0
II. Bacterial endocarditis	17.8

Table IX shows the incidence of pericarditis, either acute or in the stage of adherent pericardium, in the different groups of cases of rheumatic heart disease, and also in the cases of bacterial endocarditis. It is obvious that in the cases of rheumatic valvular deformity there had been an acute rheumatic endocarditis. It is probably fair to assume that, in the cases of old valve deformities in which there was no acute pericarditis or an adherent pericardium, there had never been an acute pericarditis, for the type of pericarditis which is associated with acute rheumatic fever (fibrinous, mainly) undergoes organization early in its course, and fibrous adhesions result. The highest incidence of peri-

cardial involvement, not including the group in which death was caused by adherent pericardium, occurred in the acute and recurrent rheumatic groups, in which it was 52.5 per cent and 41.1 per cent, respectively. In the three subgroups of valvular deformities it was 12.5 per cent, 22.2 per cent, and 14.1 per cent, respectively. Obviously, all of the patients in these three subgroups had passed through an acute stage of rheumatic endocarditis. Therefore, the incidence of pericardial involvement in these groups probably represented the clinical incidence of pericarditis better than that in the two groups in which death occurred during an attack of acute rheumatic endocarditis.

The incidence of pericarditis (17.8 per cent) in the cases of bacterial endocarditis was about the same as the average in the cases of rheumatic valvular deformities, not including the group in which death was caused by an adherent pericardium. Since the incidence of pericardial involvement in the cases of valvular deformities probably represents closely the actual clinical incidence of pericarditis in association with acute rheumatic endocarditis, and since it is nearly the same as the incidence of pericarditis in cases of bacterial endocarditis, it appears obvious that the existence of pericarditis cannot be used clinically to differentiate acute rheumatic endocarditis from bacterial endocarditis.

In not all of the cases of rheumatic heart disease was there evidence of pericarditis. The same can be said of myocarditis. The term pancarditis, although generally applicable, cannot always be used, even in autopsy cases of acute rheumatic endocarditis, and certainly less frequently clinically in cases of rheumatic heart disease.

The coronary arteries.—The degree of atherosclerosis of the coronary arteries was studied with interest, for, if the coronary arteries are involved extensively in rheumatic heart disease, a causal relation between the infection and atherosclerosis might be suspected. The degrees of coronary sclerosis mentioned in the autopsy protocols were graded from + to ++++, as nearly as possible. Grade ++++ indicated that the vessels were completely, or almost entirely, closed. A + degree represented a slight amount of sclerosis. The degrees ++ and +++ were intermediate. No sclerosis was recorded as 0.

The condition of the left and right coronary arteries, mainly the descending branches, was described. Table X shows the degree of sclerosis in the different groups of cases of rheumatic heart disease (acute rheumatic, recurrent rheumatic, healed valve deformities, subgroups "a," "b," and "c," and adherent pericardium, respectively). Of the 796 cases, in only 601 were the coronary arteries sufficiently well described to be rated. In only ten of these was the sclerosis graded ++++, as follows: three, left ++++, right +++; five, left ++++, right ++; one, left ++++, right +; and one, left ++++, right 0. These ten were in the calcified nodular group (subgroup "c"), in which death

TABLE X

DEGREE OF CORONARY SCLEROSIS

	ACUTE RHEUMATIC		RECURRENT RHEUMATIC		VALVE DEFORMITY SUBGROUP "A"		VALVE DEFORMITY SUBGROUP "B"		VALVE DEFORMITY SUBGROUP "C"		ADHERENT PERICARDIUM		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
L++++ R+++	0	0	0	0	0	0	0	0	3	1.5	0	0	3	0.5
L++++ R++	0	0	0	0	0	0	0	0	5	2.5	0	0	5	0.8
L++++ R+	0	0	0	0	0	0	0	0	1	0.5	0	0	1	0.2
L++++ R0	0	0	0	0	0	0	1	0.5	1	0.5	0	0	2	0.4
L+++ R+++	0	0	0	0	0	0	7	4.0	16	8.1	0	0	23	3.8
L+++ R++	0	0	0	0	1	1.2	3	1.7	8	4.1	1	5.0	13	2.2
L+++ R+	0	0	0	0	0	0	0	0	1	0.5	0	0	1	0.2
L+++ R0	0	0	0	0	0	0	0	0	3	1.5	0	0	3	0.5
L++ R++	1	1.5	1	1.9	8	9.0	12	6.7	16	8.1	3	15.0	41	6.8
L++ R+	0	0	1	1.9	0	0	1	0.5	7	3.6	1	5.0	10	1.7
L++ R0	1	1.5	0	0	0	0	3	1.7	3	1.5	1	5.0	8	1.1
L+ R+	9	13.8	13	24.5	30	34.0	37	20.8	45	22.8	2	10.0	136	22.6
L+ R0	1	1.5	2	3.8	3	3.4	3	1.7	5	2.6	0	0	14	2.3
L0 R0	53	81.5	36	67.9	45	51.2	110	61.8	83	42.1	12	60.0	339	56.4
L0 R+++	0	0	0	0	1	1.2	1	0.5	0	0	0	0	2	0.4
Totals	65	99.8	53	100.0	88	100.0	178	99.9	197	99.9	20	100.0	601	99.9

occurred chiefly in the upper decades, the sixth and seventh. In most of the cases of rheumatic heart disease the sclerosis of the coronary arteries was less than +++ on the left or right. This was true in all of the cases of acute rheumatic endocarditis, recurrent rheumatic endocarditis, and adherent pericardium, and also in eighty-seven (98.9 per cent) of the eighty-eight cases in subgroup "a," in 170 (95.5 per cent) of the 178 cases in subgroup "b," and in 171 (86.8 per cent) of the 197 cases of subgroup "c" (valvular deformities).

There was no suggestion of any unusual degree of coronary sclerosis in the different groups of cases of rheumatic heart disease. The greatest amount was found in subgroup "c," in which death occurred in the later decades. There was, therefore, no evidence to support the idea that rheumatic infection of the heart may increase the incidence or degree of coronary sclerosis. In fact, there was really less coronary sclerosis than in cases in which death resulted from other causes. In the same series of autopsies (27,957) from which the 796 cases of rheumatic heart disease were taken, there were 1,066 cases in which death was caused by coronary sclerosis (3.8 per cent).

SUMMARY AND CONCLUSIONS

Rheumatic heart disease, including all forms immediately or indirectly caused by rheumatic infection, was a common, but not the most frequent, type of heart disease encountered in our study of 4,254 cases in which death resulted from noncongenital heart disease (796 cases, 18.7 per cent). Rheumatic heart disease was responsible for less than one-third of the cases of noninfectious heart disease (hypertensive heart disease, coronary sclerosis, and the various types of cor pulmonale), and its incidence was the same as that of bacterial endocarditis and cardiac failure secondary to syphilitic aortitis, combined.

There are four types of rheumatic heart disease, in two of which (acute rheumatic endocarditis and recurrent rheumatic endocarditis) the characteristic verrucous or rheumatic vegetations occur on the valves. In the second of these there are evidences of previous infection and scarring of the valves. These two types were not commonly encountered at autopsy (12.3 per cent and 9.5 per cent, respectively). The third variety, comprising cases of valvular deformities, caused the greatest number of deaths (73.5 per cent). In some of these cases the lesions were completely healed, and some showed signs of lingering infection. The calcified, nodular, aortic valve deformity, which is regarded by some as nonrheumatic, is, in our opinion, a rheumatic lesion. It comprised 40 per cent of all of the valve deformities. If it were not included among the rheumatic lesions, we would have to conclude that rheumatic infection of the aortic valve is uncommon. There were only a few cases in the fourth group, that in which it could be proved definitely that death had been caused by an adherent pericardium.

Death from acute and recurrent rheumatic endocarditis occurred chiefly in the early decades. Death from the incompletely or completely healed valvular deformities took place primarily in the middle decades, and, from the calcific, nodular, aortic valve deformity, in the later decades.

The sex incidence in this series was as follows: males, twenty-seven per thousand; females, thirty-one per thousand. The females died earlier than the males. This is probably because the valve which is most commonly involved in females is the mitral. Males and females with the same valve lesions die in the same decades. With a mitral deformity, compensation cannot be maintained as long in either sex as with an aortic valve lesion.

Little evidence for or against any of the theories concerning the nature of the infectious agent in rheumatic heart disease was discovered in this study. The type of inflammatory reaction within the valve was very similar to that which occurs in cases of frank, streptococcic, subacute bacterial endocarditis. This might be regarded as evidence in favor of the streptococcic theory of the etiology of rheumatic fever. The fact that the inflammatory reaction is a proliferative one does not definitely support the virus theory. It is even questionable whether the Aschoff nodule, which varies so decidedly in structure, and is by no means constantly present in cases of rheumatic heart disease, is sufficiently characteristic to justify the suspicion that it is caused by a specific infectious agent.

The valves of the left side of the heart are the ones which are chiefly involved (99.8 per cent). In 5.6 per cent of the cases there was right-sided involvement, but in all but one of these there was also a lesion of one or both of the valves of the left side of the heart.

The aortic and mitral valves were involved with equal frequency in the males. The incidence of involvement of the aortic alone, the mitral alone, and the aortic and mitral together, in the males, and of the aortic and mitral together, in the females, was about the same. Among the females, aortic involvement was less common than mitral involvement. The predilection for the mitral valve in females is not understood, but it helps to explain why the calcified, nodular, aortic deformity is common in old men.

Vegetations begin on the side of the valve where the spongiosa layer, which contains most of the blood vessels, is located, namely, on the ventricular surfaces of the aortic and pulmonic cusps, and on the auricular surfaces of the mitral and tricuspid valves. This suggests that the infection may be embolic in origin, but, in some cases, small vessels can be seen leading from surface indentations, which would indicate that infection may occur directly from the blood stream.

Valves which are thickened and scarred from repeated attacks of proliferative inflammation show a marked tendency to become calcified.

A calcified aortic valve has the same structure as a calcified mitral valve. Our study disclosed nothing to indicate that the calcified nodular aortic valve deformity differs etiologically and pathogenetically from the calcified mitral valve.

Auricular endocardial involvement was practically as common in cases of acute rheumatic endocarditis as in bacterial endocarditis.

Hypertrophy, which appears to be caused by increased work, was present in most of the cases; it was most marked when there was aortic involvement, and less pronounced when there were mitral lesions only. More hypertrophy was noted among the males, apparently because aortic lesions are more common among males than females.

Gross areas of fibrosis were rarely seen in cases of rheumatic heart disease, and, with a few exceptions, the coronary arteries were relatively free from severe sclerosis. There was no indication that rheumatic infection bears any causal relation to coronary sclerosis.

Pericarditis, either acute or in the form of *adherent pericardium*, was not a constant accompaniment of acute or recurrent rheumatic endocarditis. It was no more common than in subacute bacterial endocarditis. The presence of pericarditis cannot be used clinically in the differential diagnosis of acute rheumatic and subacute bacterial endocarditis. Death rarely resulted from the effects of an adherent pericardium alone.

Proliferative inflammation, of a nodular (*Aschoff nodules*) or *diffuse* type, was usually present. It may result in periarterial scarring. Such inflammation, although common, was not always present in cases of acute or healed rheumatic heart disease, but it was more common during the acute stage. The stigmata of rheumatic inflammation were practically as common in the valve and myocardium in the cases of calcified, nodular, aortic valve deformities as in the cases of mitral valve deformities.

Several important facts which might be of value clinically in the study of rheumatic heart disease emerge from the analysis of these 796 cases. Rheumatic heart disease causes slightly less than 20 per cent of all deaths from noncongenital cardiac disease, which is nearly twice the number caused by bacterial endocarditis, and nearly three times as many as result from heart disease secondary to syphilitic aortitis. As a rule, patients with *acute rheumatic endocarditis* die, not during an acute attack, but later, from the effects of valvular stenosis and insufficiency. Rheumatic heart disease affects males and females in about equal numbers. The males tend to live longer than the females. The aortic and mitral valves are involved with equal frequency in males, but mitral valve involvement greatly predominates in females. This means that the incidence of aortic valve lesions is higher in males than in females, and that that of mitral lesions is higher in females than in males. Both males and females survive

longer with an aortic lesion than with a mitral. All nonsyphilitic aortic valvular deformities which lead to cardiac failure appear to be rheumatic in origin. Tricuspid and pulmonic lesions, especially healed deformities, rarely occur without an associated aortic or mitral lesion.

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THE DIAGNOSIS OF CORONARY OCCLUSION AND MYOCARDIAL INFARCTION BY FLUOROSCOPIC EXAMINATION

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ALTHOUGH it is accepted that roentgenologic examination is a valuable and often indispensable adjunct in the diagnosis of certain types of heart disease, it has received comparatively scant attention in connection with disease of the coronary arteries, particularly coronary occlusion. As recently as 1934, it was remarked[1] that "roentgen studies have not been of any assistance in localizing, or, in fact, recognizing cardiac infarcts." Although the clinical manifestations of coronary occlusion are, as a rule, characteristic, the diagnosis is occasionally uncertain, and it is frequently difficult to evaluate the extent of myocardial involvement after recovery from the acute attack. Ordinary roentgenologic examination is of little help, for myocardial infarction, even when it is extensive, does not alter the cardiac contour unless marked enlargement or a ventricular aneurysm has resulted. However, roentgenologic methods which enable one to watch ventricular contraction offer greater promise, and it is the object of this report to show that impaired contraction of the left ventricle can be detected by simple fluoroscopic examination in a majority of cases of occlusion of a coronary artery.

That coronary occlusion produced changes in myocardial contraction was recognized experimentally as early as 1698, by Chirac,[2] and by a number of investigators[3-7] in the nineteenth century. However, a detailed description of these changes was lacking previous to the recent investigation of Tennant and Wiggers.[8] Employing the myocardiograph, they found that, immediately after occluding branches of the coronary arteries, in dogs, the area of muscle which was rendered ischemic ceased to contract, and paradoxical (reverse) movements occurred, i.e., the ischemic area bulged passively while the remainder of the ventricle contracted normally.

In man, the movements of the heart can be studied by means of fluoroscopy or roentgenkymography. There have been few recorded fluoroscopic observations of the effect of coronary artery occlusion on the contractile movements of the heart, except when the infarct has been extensive enough to result in the formation of a ventricular aneurysm. Impaired pulsation and systolic expansion have frequently been recognized fluoroscopically in such cases.[9-13] Libman[13] and Levene and

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his coworkers[14] observed localized impairment of contraction of the left ventricle in cases of coronary artery disease, but did not describe the systolic expansion (reversal of pulsation) which we found in fifty per cent of our cases of coronary occlusion,[15, 16] and which we consider pathognomonic of infarction. The senior author[16] has used fluoroscopic means of detecting coronary occlusion routinely for at least five years. Roentgenkymographic studies, also, have indicated that systolic expansion of the infarcted area characteristically occurs.[17, 18]

MATERIAL STUDIED

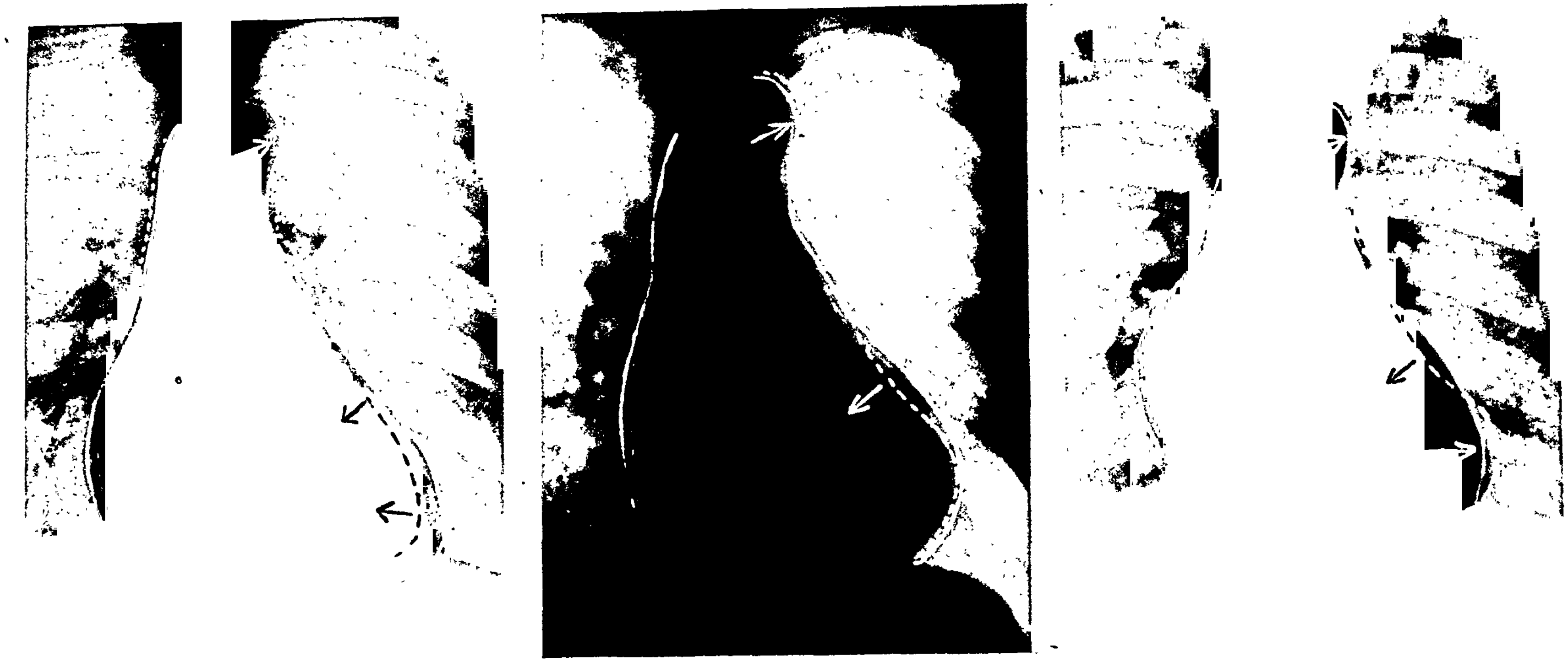
A fluoroscopic and roentgenkymographic study of ninety-five patients was made; this series comprised eighty cases of coronary occlusion and fifteen cases of coronary sclerosis and angina pectoris. The roentgenkymograms were taken immediately after the fluoroscopic examination. For control purposes, a large number of normal subjects were examined fluoroscopically, and, in thirty-five of these, roentgenkymograms were obtained. The patients with coronary occlusion were studied at intervals ranging from one month to six years after the acute attack. In twenty-four subjects with normal hearts or with cardiac infarcts, cineroentgenographic studies were made.

TECHNIQUE

A Patterson B-type fluoroscopic screen was employed, with the usual illumination for fluoroscopy (70-80 K.V. and 4 to 5 Ma.). Proper accommodation was found to be essential for study of the cardiac movements. After inspection of the size, shape, and position of the heart and great vessels, the size of the fluoroscopic screen was reduced so that it included only the left border of the heart. The time relationship of the pulsations was established by comparing the movements of the left ventricle with those of the aorta and pulmonary artery. Normally, the arterial pulsations are opposite in phase to those of the ventricle; the aorta expands while the ventricle contracts, and there is an inthrust of the entire left ventricular border, together with elevation of the apex and diaphragmatic surface of the heart (Fig. 1*A*). The medial movement of the upper part of the left ventricular border may slightly precede the inthrust of the apical region. Following examination in the posteroanterior position, the subject was rotated by degrees into the left oblique position, and the movements of the lateral and posterior walls of the left ventricle were studied successively.

The contractile movements of the heart were observed at the end of a moderately deep inspiration. In addition to immobilizing the diaphragm, this procedure slows the heart rate, and thus facilitates the examination, for a rapid heart rate makes it difficult to visualize the ventricular movements in detail. The patient was instructed not to strain, for this, by increasing intrathoracic pressure, may decrease the venous return to the heart and thereby reduce ventricular ejection and pulsation.

Several maneuvers may be employed when the details of the cardiac movements are not very clear. It is occasionally helpful to magnify the movements by drawing the screen away from the patient, particularly when the pulsations are of small amplitude. The presence of apical pericardial fat may obscure contraction and give the impression of diminution or absence of pulsation; one must therefore look within the fat pad to observe the ventricular movements. Since the study of ventricular pulsation is concerned even more with uniformity of contraction along the left ventricular border than with the amplitude of contraction, orientation as to time of contraction is of utmost importance. This may be attained by auscultation; a Bowles diaphragm is held to the patient's chest in the fourth intercostal space. Normally, the inthrust of the ventricle is synchronous with the first heart sound.



A. B. C.

Fig. 1.—Outline of the heart and great vessels in systole and in diastole, as determined by fluoroscopy. The unbroken line represents diastole, the *dotted line*, systole. *A*, Normal contraction. The left ventricle contracts uniformly in systole, with expansion of the aorta and pulmonary artery. *B*, Impaired contraction. While the upper half of the left ventricular border contracts normally, practically no pulsation is visible over the lower left ventricular border within the infarcted area. *C*, Reversal of pulsation (systolic expansion). There is loss of uniformity of left ventricular contraction. While the upper part of the left ventricular border contracts normally, the infarcted area above the apex does not contract, but is passively expanded by the elevated intraventricular pressure during systole.

When the heart rate is rapid, temporary slowing may be induced by pressure on the carotid sinus; this increases the magnitude of ventricular contraction and facilitates the examination.

The roentgenkymograms were obtained with a multiple-slit lead grid of the type described by Stumpf.[19] The slits were 12 mm., and, in some cases, 18 mm., apart, thereby visualizing the pulsations of points at closely spaced intervals along the heart border. The duration of exposure was 1.5 seconds, so that one to three complete cardiac cycles were recorded, depending on the heart rate. Exposures were taken in the posteroanterior and left oblique (about 25°) positions.

Motion pictures (Fig. 2) were made with a standard camera which had a film speed of 16 exposures per second. Intense illumination of the fluoroscopic screen was necessary for good photographic contrast. The roentgen factors were 75 Ma. at 100 K.V. for an exposure of two to three seconds. The film was serially reprinted for motion picture projection, which permitted a longer strip to be studied.

RESULTS

Coronary Occlusion.—Localized abnormalities in pulsation were observed fluoroscopically in fifty-nine (73 per cent) of the eighty cases of myocardial infarction. These consisted of complete or partial reversal of contraction in forty cases (50 per cent), and absence or diminution of pulsation in nineteen (23 per cent) (Table I).

TABLE I

TYPES OF VENTRICULAR CONTRACTION IN EIGHTY CASES OF CARDIAC INFARCTION

	FLUOROSCOPICALLY		ROENTGENKYMOGRAPHICALLY	
1. Normal	21		16	
2. Reversal of Pulsation	40		42	
a) complete		29		25
b) partial		11		17
lag		8		7
doubling		3		10
3. Impaired Pulsation	19		22	
a) absent		2		7
b) diminished		17		15
Total	80		80	

Reversal of pulsation was the most common and definite abnormality in ventricular contraction associated with myocardial infarction. It was recognized by a loss of uniformity of contraction along the left ventricular border; as the normal portion of the ventricle contracted synchronously with the expansion of the great vessels during systole, the weakened myocardium at the site of the infarct was seen to expand passively as a result of the sudden rise in intraventricular tension (Figs. 1*C* and 2). This abnormality frequently appeared as a wavelike movement along the border of the left ventricle (Fig. 1*C*). Similar observations were made in three cases of ventricular aneurysm. In twenty-nine cases the reversal of pulsation was complete; in eleven others it was incomplete, and appeared only as a localized lag of systolic inthrust, or as a double systolic pulsation. Localized diminution or complete absence of

pulsation was also frequently observed (Fig. 1*B*), but these changes were less definite and significant than the systolic expansion.

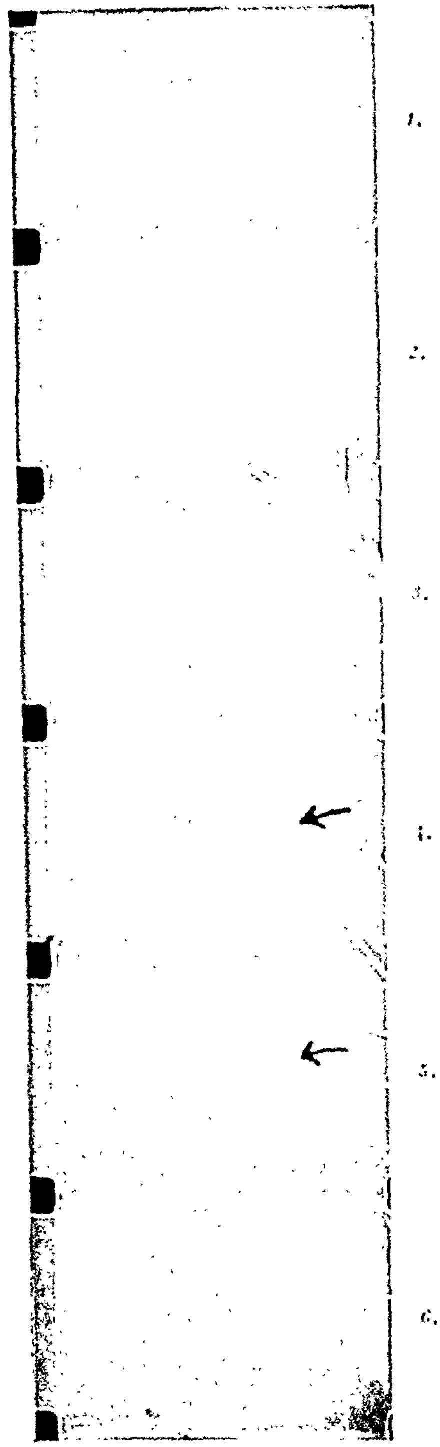


Fig. 2.—Continuous strip from cineroentgenograms in a case of cardiac infarction. Frames *1*, *2*, and *3* represent the heart in diastole. During systole, shown in frames *4* and *5*, there is a localized bulge of the left ventricular border above the apex which results from passive expansion of the infarcted area by the heightened intraventricular pressure. With the end of *systole* (frame *6*), as the intraventricular pressure abruptly falls, reducing the tension on the infarcted area, the left border again resumes an unbroken contour.

The abnormalities in contraction were most common over the lower left ventricular border, particularly in the apical and supra-apical regions (Fig. 3). In a few cases the changes were limited to the mid-region and upper section of the left ventricular border. The abnormalities were observed more frequently and with greater certainty in the posteroanterior than in the left oblique view; rarely, they were limited to the latter view. Thus, of the fifty-nine cases in which there was an abnormal pulsation, it was seen in the posteroanterior view alone in thirty-eight cases, in both posteroanterior and left oblique views in eighteen cases, and in the left oblique view alone in only three cases.

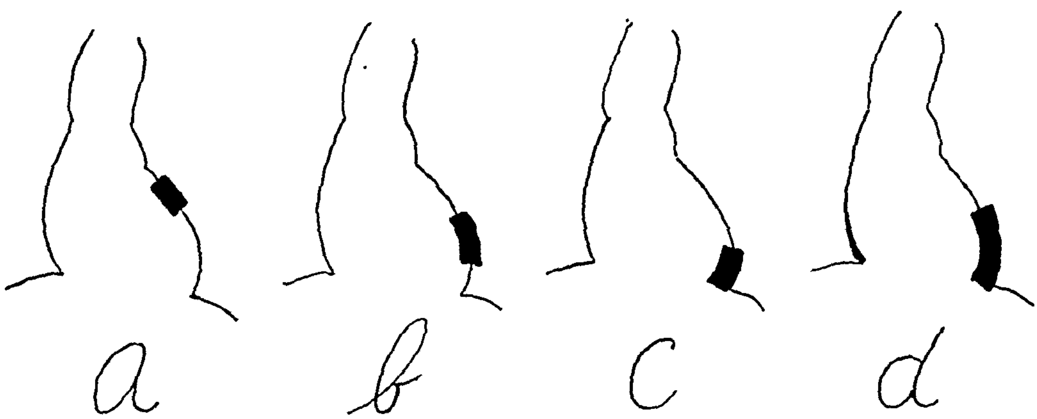
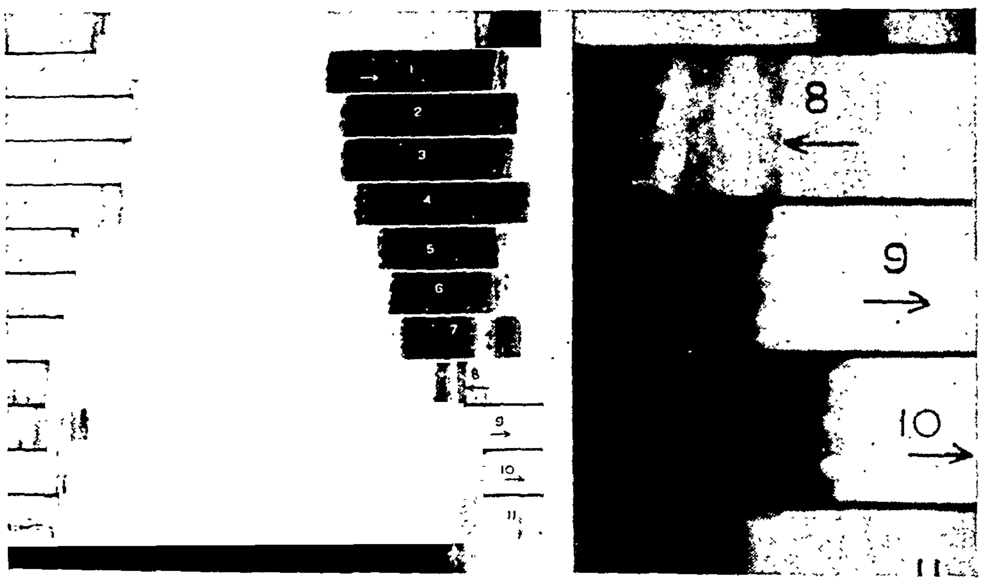


Fig. 3.—Location of abnormal pulsations fluoroscopically. *a*, Upper region of left ventricular border (4 cases); *b*, Supra-apical segment of left ventricle (17 cases); *c*, Apex of left ventricle (13 cases); *d*, Lower half of left ventricular border (25 cases).

Similar abnormalities in left ventricular pulsation were revealed by kymographic examination (Fig. 4). Comparison of the fluoroscopic and roentgenkymographic observations in the posteroanterior position showed complete agreement between the two methods in sixty-seven of the eighty cases. In five cases, definite abnormalities were present in the kymogram which were not detected fluoroscopically. In only one case was the kymogram normal when the fluoroscopic findings were considered abnormal; however, in this instance the pulsation was merely diminished, not reversed. In the remaining seven cases both the fluoroscopic and kymographic examinations revealed an abnormal pulsation, but there was some discrepancy in the interpretation of the type of abnormality. For example, in several cases what was interpreted fluoroscopically as absence of pulsation appeared in the kymogram as reversal; in another instance, what seemed to be a lag fluoroscopically turned out to be a reversal in the kymogram. In the left oblique position fluoroscopic examination was somewhat less satisfactory, and in nine cases abnormalities which were recorded in the kymogram were not detected with the fluoroscope. In general, it is evident that the results of the two methods agreed well in all of their essentials. When the fluoroscopic results were not confirmed by the kymograph, the error was usually one of omission rather than commission.

An attempt was made to correlate the fluoroscopic observations with the electrocardiographic localization of the infarct (Table II). Electrocardiographically, the cases were divided into four groups: anterior wall infarction, thirty-eight cases; posterior wall infarction, sixteen; anterior and posterior wall infarction, thirteen; and atypical pattern, thirteen. Of the thirty-eight cases of anterior wall infarction, in twenty-two there was an abnormal ventricular contraction which was observed in the posteroanterior position in every instance, and also in the left oblique view in four of the cases. When there was infarction of the posterior wall, or of both anterior and posterior walls, the abnormal pulsation was seen in the left oblique position, as well as in the postero-anterior, in almost half of the cases. Although these observations suggest that abnormal contraction is frequently observed in the left oblique view when the infarct is situated on the posterior wall of the left ventricle, it should be emphasized that only rarely is the abnormality confined to this view, e.g., in only three of our cases.



A. *B.*

Fig. 4.—*A*, Roentgenkymogram from a patient with an old infarct of the anterior surface of the left ventricle, exhibiting the various types of abnormalities in left ventricular contraction. *B*, Magnification of movements of left ventricular border.

Segment *8*.—Normal ventricular contractions. There is an inward (mesial) movement of the upper portion of the left ventricle synchronous with outward (lateral) movement of the aorta (segments *1* and *2*).

Segment *9*.—Partial reversal of pulsation. The left ventricular border contracts in early systole, but immediately thereafter shows a lateral movement (systolic expansion). This appears fluoroscopically as a double systolic pulsation.

Segment *10*.—Complete reversal of pulsation. The mid-ventricular border shows a systolic expansion (lateral movement) which is synchronous with the normal mesial movement of segment *8* and with the expansion of the aorta.

Segment *11*.—Complete absence of pulsation of left ventricular border in the apical region.

Coronary Sclerosis.—Fluoroscopic studies were made on fifteen patients who had either a history of angina pectoris or electrocardiograms which suggested coronary artery disease, but gave no history of acute coronary occlusion. In ten cases the ventricular contractions were en-

TABLE II

COMPARISON OF ELECTROCARDIOGRAPHIC AND FLUOROSCOPIC LOCALIZATION OF INFARCTION

	ELECTROCARDIOGRAPHIC LOCALIZATION							
	ANTERIOR WALL		POSTERIOR WALL		ANTERIOR AND POSTERIOR		ATYPICAL PATTERN	
	F*	K*	F	K	F	K	F	K
Location of Abnormal Pulsation								
Normal	16	11	3	2	1	2	1	1
Posteroanterior View	22	27	11	11	12	11	11	11
a) upper left vent. border	0	1	1	1	1	1	0	0
b) supra-apical segment	8	7	3	4	2	1	4	4
c) apex	4	6	3	1	4	2	2	3
d) lower half left vent.	10	13	4	5	5	7	5	4
Left Oblique View	4	4	4	7	8	9	5	5
a) upper left vent.	0	0	2	4	2	2	0	1
b) lower left vent.	4	4	2	3	6	7	5	4

*F is fluoroscopy; K is kymography.

tirely normal fluoroscopically and in the kymograms. In two cases equivocal changes were observed by both methods. Of the remaining three cases, absence and partial reversal of pulsation were seen fluoroscopically in two, and were present in the kymogram in all. Although these patients had practically normal electrocardiograms, in each case a severe anginal syndrome was present, and it is probable that extensive myocardial disease accounted for the partial reversal.

Normal Subjects.—No abnormal pulsations were observed in the large control group of normal subjects who were examined fluoroscopically, and roentgenograms in thirty-five of these subjects were normal.

COMMENT

It is evident from these results that fluoroscopic examination affords a relatively simple and accurate method of detecting the presence of a myocardial infarct. Abnormalities in ventricular contraction may be observed in nearly three-fourths of the cases of coronary artery occlusion; they appear as a localized reversal (systolic expansion) in half of the cases, and as absence or diminution of pulsation in about one-fourth. The former has greater significance than the latter and may be considered pathognomonic of myocardial infarction. The reversal of pulsation is probably caused by a bulging of the weakened, infarcted area; this area is thrust outward by the systolic rise of intraventricular pressure, while the remainder of the ventricle contracts forcibly. The reversal may not be complete; it then appears as a localized lag of systolic contraction, or as a double systolic pulsation. Since, in normal persons, the inthrust of the upper left ventricular border slightly precedes that of the apex,[20] a slight lag of the supra-apical region must be interpreted with caution. Localized diminution or absence of pulsation must be regarded as abnormal, but not pathognomonic of infarc-

tion, and should not be confused with a normal apical pulsation which is obscured by a pericardial fat pad.

Although we think that reversal of pulsation is pathognomonic of myocardial infarction, we have observed it in a small number of cases of aortic valvular disease and long-standing hypertensive heart disease in which there was considerable cardiac enlargement. These abnormalities occurred chiefly when cardiac insufficiency and precordial pain were present, so that, although they were probably not indicative of actual infarction, it is likely that they were caused by myocardial disease. It is possible that there was an aneurysmal thinning of the myocardium in the apical region in these cases. Esser[21] noted impairment of apical contraction in cases of cardiac enlargement of all types.

Among the cases of myocardial infarction, the apical and supra-apical regions of the left border, that is, the anterior wall of the left ventricle, most frequently exhibited abnormal pulsation when either the anterior or the posterior wall was involved. Fluoroscopic examination, therefore, is not decisive in localizing the area of infarction, and it appears that the area of abnormal contraction does not always correspond to the area of infarction. The probable explanation for this is that damage at any point to the deep and superficial spiral muscles, which wind around the apical region of the left ventricle, may alter the leverage in contraction in such a way as to produce an abnormal type of pulsation at the apex. However, abnormal contractions in the left oblique position, as well as in the posteroanterior view, are more likely to occur with infarction of the posterior wall than with anterior wall infarction.

Our studies indicate that the results obtained fluoroscopically closely parallel those of roentgenkymography. In the few cases in which these methods disagreed, an abnormal pulsation was present in the kymogram but was not detected fluoroscopically. Although roentgenkymography has the advantage of being an objective method, it requires special apparatus and some experience in interpretation. Fluoroscopic examination, on the other hand, is a simple method which is available to all who are engaged in clinical medicine. Furthermore, it enables one to study the movement of the entire left ventricular border by gradually rotating the patient and making observations at different angles, whereas in the kymogram the movements of only one projection, or at most a few, are recorded. Thus, in one case, reversal of pulsation was detected fluoroscopically over the lower left ventricular border with the patient rotated in the left oblique position to an angle of 15° to 20°, but was not observed in other views, and roentgenkymograms which had been taken in the posteroanterior and full left oblique positions failed to reveal this abnormality. When a kymogram was taken at the proper angle, the reversal of pulsation was clearly recorded. Similarly, an aneurysm of the apex of the left ventricle was brought out fluoroscopically by rotating the subject slightly into the right oblique position.

The ideal procedure would be to make a fluoroscopic examination first, and then take roentgenkymograms at those projections in which abnormal pulsations of the left ventricular border are suspected.

Although contraction becomes impaired immediately following myocardial infarction, fluoroscopic examination is not likely to find wide application in the acute stage of coronary occlusion, for the patients are usually too ill for such examination. Occasionally, however, it may be helpful when the diagnosis is difficult, as in cases of progressively increasing angina pectoris, or when there are mild, atypical attacks. A problem of greater importance is to evaluate the extent of myocardial involvement immediately following recovery from an acute attack of coronary occlusion, and to detect the presence of infarction in patients who give a past history of such an attack, or of angina pectoris. Although the electrocardiogram is helpful in these cases, it is often inadequate, and further diagnostic aids, such as fluoroscopy, are welcome.

SUMMARY AND CONCLUSIONS

Fluoroscopic examination in a group of eighty patients with cardiac infarcts secondary to coronary artery occlusion revealed abnormalities in the contraction of the left ventricle in fifty-nine cases, or 73 per cent. This was evident as a localized impairment of pulsation along the left ventricular border which was best observed in the ordinary posterior anterior view, and most often in the apical, and particularly the supra-apical, region.

The abnormalities consisted of (a) complete reversal of pulsation (systolic expansion) (twenty-nine cases); (b) partial reversal, which appeared as a lag, or doubling, of systolic contraction (eleven cases); (c) absence of pulsation (2 cases); and (d) marked localized diminution of pulsation (seventeen cases).

An abnormal pulsation was seen in two out of fifteen cases of coronary sclerosis and angina pectoris in which there was no history of coronary occlusion. These abnormalities were not observed in any of a large group of subjects without heart disease who were examined as controls.

The fluoroscopic abnormalities corresponded closely with those observed in the roentgenkymograms which were taken immediately after the fluoroscopic examination in all cases. Cineroentgenograms, which were taken in twenty-four cases, also demonstrated the different types of abnormal pulsations.

A localized reversal of pulsation (systolic expansion) is considered pathognomonic of infarction when the heart is not considerably enlarged. When the heart is enlarged, the pulsations may be impaired near the apex in the absence of cardiac infarction, but even in such cases complete systolic expansion is only rarely observed.

It is concluded that fluoroscopic examination is a valuable and reliable method for detecting cardiac infarction following coronary artery

occlusion. The method is not advocated for use during the first days of the illness, but rather to help evaluate the degree of myocardial involvement after recovery from the acute attack. Since the changes in contraction may be permanent, fluoroscopic examination may be the means of obtaining evidence of previous infarction in patients with angina pectoris, or in any patient whose history suggests that he has had an attack of coronary artery occlusion.

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THE EFFECTS OF WHOLE BILE AND BILE SALTS ON THE INNERVATED AND THE DENERVATED HEART

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THE effect of whole bile and bile salts on the perfused heart was reported recently by the authors.[1] The results obtained indicated that there is a direct action of these agents on the myocardium. However, since the slowing of the heart of the intact animal and other changes in rhythm which are produced by bile constituents have been attributed, by some authors, to vagal reflexes, it seemed desirable to compare the effect of the administration of whole bile and of bile salts on the innervated and the denervated heart in otherwise intact animals. In this paper we are reporting the results of a study of the blood pressure, heart rate, and electrocardiographic changes after the intravenous administration of whole bile and bile salts to dogs with innervated hearts and to others with denervated hearts. In order to eliminate the influence of anesthetic agents, a few experiments also were performed on trained dogs.

Still[2] found that neither the administration of atropine nor double vagotomy materially changed the effect on the vascular system of administering bile constituents intravenously to dogs. Baltaceano and Vasiliu[3] indicated that the hypotensive effect of sodium taurocholate was produced through the reflexogenic zones of the carotid sinus and the cardio-aortic region. Nevertheless, they stated that bradycardia could be produced by direct action of sodium taurocholate on the myocardium, as well as reflexly through the carotid sinus. Buchbinder[4] produced obstructive jaundice in pups by ligating the common bile duct, and attributed the resulting bradycardia to a reflex through the vagus. He stated that inversion of the T wave was the most frequent abnormality which appeared in the electrocardiogram. He did not detect any prolongation of either the P-R interval or the QRS complex. Horrall[5] stated that Röhrig cut the vagi, and that Landois was the first to give bile intravenously following section of the vagi and sympathetic nerves. Röhrig[6] found that the intravenous injection of bile caused slowing of the heart before, as well as after, cutting the vagi. However, the slowing was slight after the vagi were cut. He concluded that the bile damaged the excitomotor ganglion of the heart. Landois[7] produced slowing of the heart by the intravenous administration of bile after having sectioned the vagi and sympathetic nerves, and concluded that the bile acted directly on the heart.

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METHODS

Two series of acute experiments were performed on apparently normal dogs, which weighed from 10 to 18 kg. The animals were anesthetized by the intravenous administration of 25 mg. of pentobarbital sodium (nembutal) per kilogram of body weight. All of the procedures were the same in the two series of acute experiments, except that in one group of animals bilateral denervation of the heart was done, according to the method of Cannon, Lewis, and Britton,[8] immediately after anesthesia had been induced. After the operation was completed, the animals breathed without aid.

The femoral artery was cannulated, and the blood pressure was recorded by a standard mercury manometer and kymograph. A sufficient quantity of bile for all of the experiments was collected, with aseptic technique, from the gallbladders of dogs, and filtered through sterile gauze into a sterile flask. Five per cent solutions of each of the bile salts, sodium taurocholate and sodium glycocholate, were made in Ringer's solution. The bile and the solutions of bile salts were given intravenously in appropriate doses. The blood pressure was recorded continuously, and electrocardiograms were taken before, during, and after each injection throughout each experiment.

At the end of each experiment, pieces of cardiac tissue were removed and fixed in formalin for histologic study.

In order to obtain a series of observations which could not have been influenced by anesthesia, operative trauma, or an accumulative effect of repeated doses of bile, similar experiments were performed on a group of trained dogs over a period of several weeks. To make it possible to measure the blood pressure in the carotid artery repeatedly, over long periods, animals were prepared in the following manner: Aseptically, under ether anesthesia, both carotid arteries were separated carefully from the carotid sheaths for a distance of about 5 cm. The muscles surrounding each carotid sheath were sewed together dorsad to the vessels in such a way that the arteries lay superficially under the skin, making their pulsations easily palpable. The dogs made an uneventful recovery, and, after training, would lie quietly on the table. Records of both systolic and diastolic blood pressures were obtained by the method of Hamilton, Brewer, and Brotman,[9] and electrocardiograms were taken simultaneously before, during, and after the injection of bile into the lateral saphenous vein.

In order to observe the effects of the injection of bile on the denervated heart of the trained animal, the heart of one animal was denervated several weeks before the subcutaneous transposition of the carotid arteries. After the dog had recovered completely from both operations, it was trained to lie quietly on the table during the simultaneous recording of the blood pressure and electrocardiogram before, during, and after each injection of bile.

RESULTS

A prompt decrease in blood pressure followed every effective dose of bile or bile salts in the acute experiments. With repeated doses, the blood pressure was gradually reduced below the effective physiologic level. The gradual decrease in blood pressure which resulted from the successive doses of bile or bile salts was practically the same in dogs with denervated hearts as in those with innervated hearts (Table I). The only noticeable difference was that in dogs with innervated hearts the blood pressure after injection usually tended to return to its previous level, whereas in the ones with denervated hearts it did not.

The results of the experiments on the trained dog were similar. When repeated doses of whole bile, ranging from 0.25 c.c. to 1.0 c.c. per kilo-

gram of body weight, were given intravenously, over a period of several days, no marked decrease in blood pressure resulted until a dose of 1 c.c. per kilogram of body weight was given (Fig. 1). The rate of both the denervated and the innervated heart slowed markedly under the influence of the large doses of bile, in spite of the fact that a slight, transient tachycardia followed the initial, small doses. Different types of cardiac irregularities were recorded in the electrocardiograms. In several experiments cardiac standstill was observed for several seconds, soon after the administration of a large dose of the bile constituent (Fig. 2).

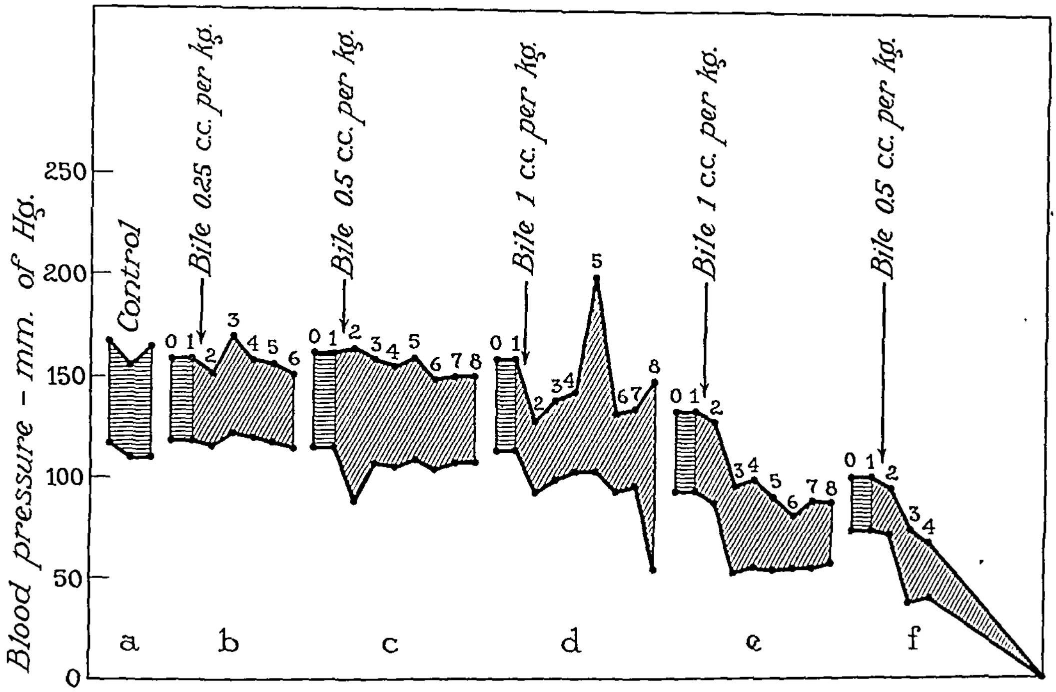

Fig. 1.—Systolic and diastolic blood pressures, measured by puncturing the carotid artery of a trained dog with an innervated heart, showing the effect of the intravenous administration of whole bile from a dog's gallbladder. Observations were made at intervals over a period of several days. The *upper border* of the curve represents the systolic, the lower, the diastolic, and the shaded area, the pulse pressure, on the same dog. *a* represents the control pressure, taken on three different days before any bile was administered. *b, c,* and *d* represent the observations made on one day. *e* and *f* were taken on the same day, because, after the injection of bile in *c*, the animal went into coma, and did not wake up even in two hours after the injection. Then blood pressure records were taken again, and a smaller dose of bile was given; a few additional records were made before the animal died. *0* to *1* represents the level of the pressure record on the same day, immediately before the injection of bile. The arrow indicates the intravenous injection of the bile, and the subsequent numbers, *2, 3, 4,* and so forth, indicate blood pressure records which were taken, respectively, at half-minute intervals after the injection.

At necropsy the heart appeared flabby and dilated. Histologic examination revealed rupture of small vessels and interstitial hemorrhages into the myocardium. In a few sections there was only evidence of congestion of vessels, with moderate to severe dilatation. Centrifugalization of specimens of blood revealed various degrees of hemolysis.

SUMMARY

The effects of the intravenous administration of whole bile and bile salts on the blood pressure and the electrocardiogram were studied

in a series of acute experiments, under pentobarbital sodium (nembutal) anesthesia, on normal dogs and on dogs with denervated hearts; the same methods and technical procedures were employed in both cases. Similar observations were made over a period of several weeks on normal, trained dogs, and on one trained dog with a denervated heart; this permitted us to make repeated observations which could not have been influenced by anesthesia, operative trauma, or an accumulative effect of successive injections of bile.

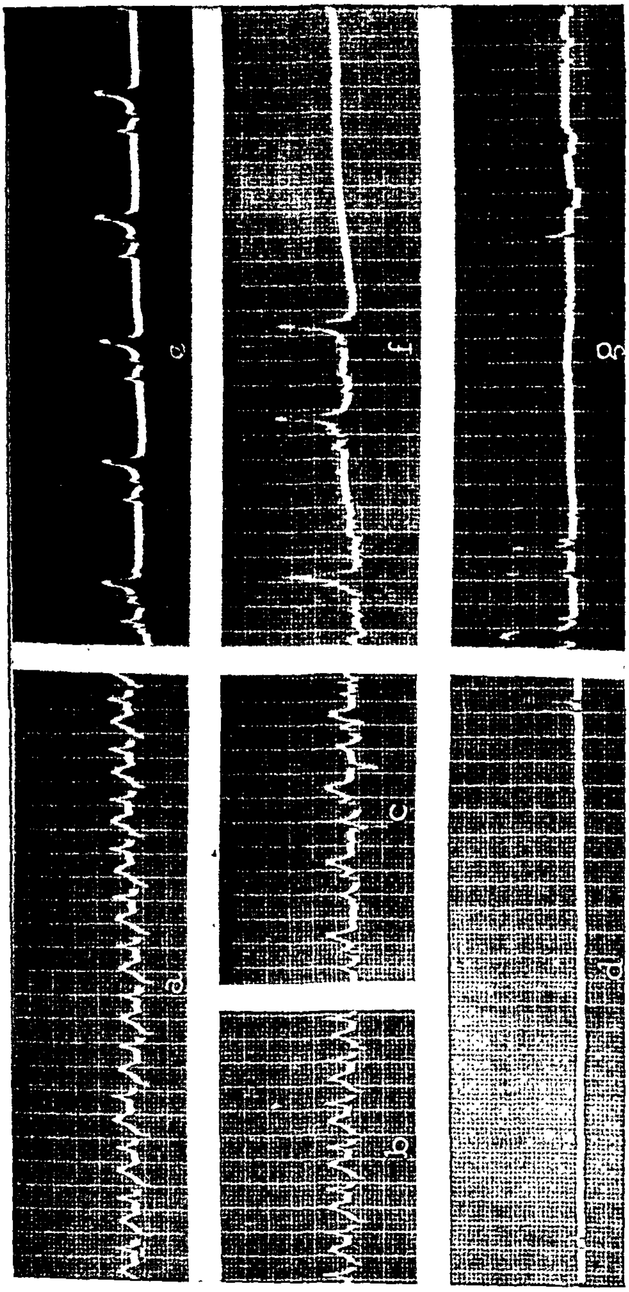

Fig. 2.—Electrocardiograms (Lead II) from a dog with innervated heart under the influence of bile, from a dog's gallbladder, which was administered intravenously. Tracings were made: *a*, before any bile was given; *b*, immediately after administration of 0.25 c.c. of bile per kilogram of body weight; *c*, immediately after administration of 0.8 c.c. of bile per kilogram of body weight; *d*, immediately after administration of 1 c.c. of bile per kilogram of body weight. The heart stopped for twenty-eight seconds, after which it resumed activity at a slow rate, as seen in *e*; *e*, five minutes after *d*; *f*, eight minutes after *d*; note the marked slowing; *g*, fourteen minutes after *d*; note the irregularities.

There were no detectable electrocardiographic differences between the effects of whole bile and bile salts on the innervated and the de-

TABLE I

REPRESENTATIVE DATA OBTAINED FROM ACUTE EXPERIMENTS ON THE INNERVATED AND DENERVATED HEART

DOSE PER KG. OF BODY WEIGHT	HEART RATE PER MINUTE		BLOOD PRESSURE, MM. OF MERCURY			
			INNERVATED HEART		DENERVATED HEART	
	INNERVATED HEART	DENERVATED HEART	BEFORE EACH INJECTION	AFTER EACH INJECTION	BEFORE EACH INJECTION	AFTER EACH INJECTION
Control	200	150	124	---	128	---
Sodium glycocholate, mg.						
29	170	150	124	114	128	102
37	160	150	128	102	138	106
45	160	150	126	103	134	100
56	180	150	120	92	126	88
63	170	140	115	78	110	86
67	160	140	108	74	102	80
74	140	140	104	61	90	70
74	130	130	96	50	76	62
74	110	120	74	38	82	58
74	110	110	60	33	58	50
74	110	100	60	[illegible]	60	44
82	70	90	46	25	62	52
85	20	80	47	0	60	50
92	35	40	36	0	[illegible]	44
Control	130	130	148	---	134	---
Sodium taurocholate, mg.						
29	140	150	148	134	134	132
35	140	150	148	144	147	121
43	140	150	152	146	143	116
53	170	140	158	136	144	108
61	150	130	152	138	140	108
64	150	150	158	140	146	112
71	160	160	163	106	154	116
71	160	160	154	135	160	132
71	160	140	160	128	154	120
71	170	150	162	123	138	104
71	180	150	150	120	160	104
71	170	150	152	106	151	96
79	160	150	133	97	128	80
82	150	140	136	76	102	66
89	130	140	122	60	91	53
89	90	120	118	49	73	49
89	40	120	106	33	54	43
89	10	100	50	22	36	30
89	?	60	47	22	20	13
Control	150	140	130	---	124	---
Bile, c.c.						
0.25	180	150	130	84	124	82
0.50	160	150	136	93	156	84
0.70	180	150	130	88	125	78
0.80	150	150	110	56	98	56
1.00	100	140	96	50	75	53
1.00	30	80	84	0	51	42

nervated heart; the irregularities and slowing of the rate of the heart were similar. During the period of gradual recovery from the hypotensive effect brought about by the first injections of bile constituents, the blood pressure of the dogs with denervated hearts usually did not return to its previous level, but the blood pressure of the dogs with innervated hearts, usually tended to do so. In both the normal animals and those with denervated hearts, approximately the same, gradual, hypotensive effect was produced by the intravenous administration of repeated doses of whole bile or bile salts. The injections finally led to failure of the heart, fall of blood pressure, and death of the animal.

Our observations on the innervated heart differed so slightly from those on the denervated hearts of otherwise intact dogs to which whole bile or bile salts were administered intravenously, that it appears justifiable to conclude that whole bile and bile salts can produce practically the same hypotensive effect and cardiac changes, such as bradycardia and disturbances in rhythm, in the absence, as well as in the presence, of the cardiac autonomic nerves.

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Department of Clinical Reports

MITRAL STENOSIS AS A CAUSE OF ANGINA PECTORIS

Report of Two Cases, With Necropsy

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RHEUMATIC aortic insufficiency has long been recognized as a cause of angina pectoris. There are, however, singularly few case reports of mitral stenosis in association with angina, and in some of these the anginal syndrome was attributed to independent disease. Although the diagnosis of mitral stenosis offers little difficulty, Gallavardin[1] has said that before one can hold that lesion responsible for the pain, it is necessary to demonstrate post mortem that there was no other.

Kourétas,[2] in 1924, culled from the literature only three cases of angina pectoris in which uncomplicated mitral stenosis was diagnosed at autopsy. To these must be added those of Levine[3] (one case), Sternberg[4] (one case), Telia[5] (one case, with microscopic studies of coronary arteries), and Hochrein[6] (one case). Cases in which no autopsy was done have been reported since 1923 by the following: Kourétas[2] (eleven cases from Gallavardin's service); Montes-Pareja[7] (one case); Castex and Beretervide[8] (four cases); Liesch[9] (two cases); Hochrein[6] (two cases); Doumer[10] (one case); Alvarez and Velasco[11] (one case); Lian, et al.[12] (two cases), and Chapuy and Brun[13] (one case).

Of the various theories which have been advanced to explain angina pectoris in cases of mitral stenosis, that of a failing heart muscle is the simplest, and therefore seems to me to be the most probable. That is to say, the right ventricle and left atrium, which are taxed to force blood through the stenosed mitral orifice, are unable to meet unusual demands; the left ventricle is therefore unable to sustain a high enough head of pressure in the root of the aorta to supply the coronary arteries with a sufficient amount of oxygenated blood.

REPORT OF CASES

Case 1.—B. T. was born in 1916, and was the second of eleven children. During the first two months of this pregnancy her mother was ill with pneumonia.

When she was six months old she had a cold, and cyanosis and dyspnea were then observed for the first time. Thereafter, marked cyanosis was occasionally observed after exertion, or in association with infections of the respiratory tract. Palpitation, shortness of breath, and precordial aching were brought on regularly by exertion, and not infrequently she experienced severe, stabbing, retrosternal pain. She felt tired constantly. After walking half a mile to school, she always had to

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rest for several minutes before she could go upstairs; at times it was necessary for her to stop and lie down. She coughed up blood occasionally, usually when she was having an unusual amount of dyspnea; she had not, however, experienced epistaxis. She suffered a great deal with migraine.

Examination.—B. T. was first examined by me in 1931. She was a poorly developed, poorly nourished girl, and was slightly cyanotic. Moderate kyphosis and precordial bulging were noticeable. A diastolic thrill was palpable just within the apex, and a diastolic shock was felt in the pulmonary area. The area of cardiac dullness was increased. At the apex, a low-pitched, rumbling murmur, beginning in mid-diastole, was followed by a long, harsh, systolic murmur which was transmitted medially. The pulmonic second sound was extremely accentuated, but there was no murmur in the pulmonic region. The systolic murmur could be heard faintly in the left interscapular space. During the period of hospitalization the pulse rate ranged from 74 to 150; it was usually between 110 and 120. The systolic blood pressure varied from 98 to 104, and the diastolic from 72 to 76.

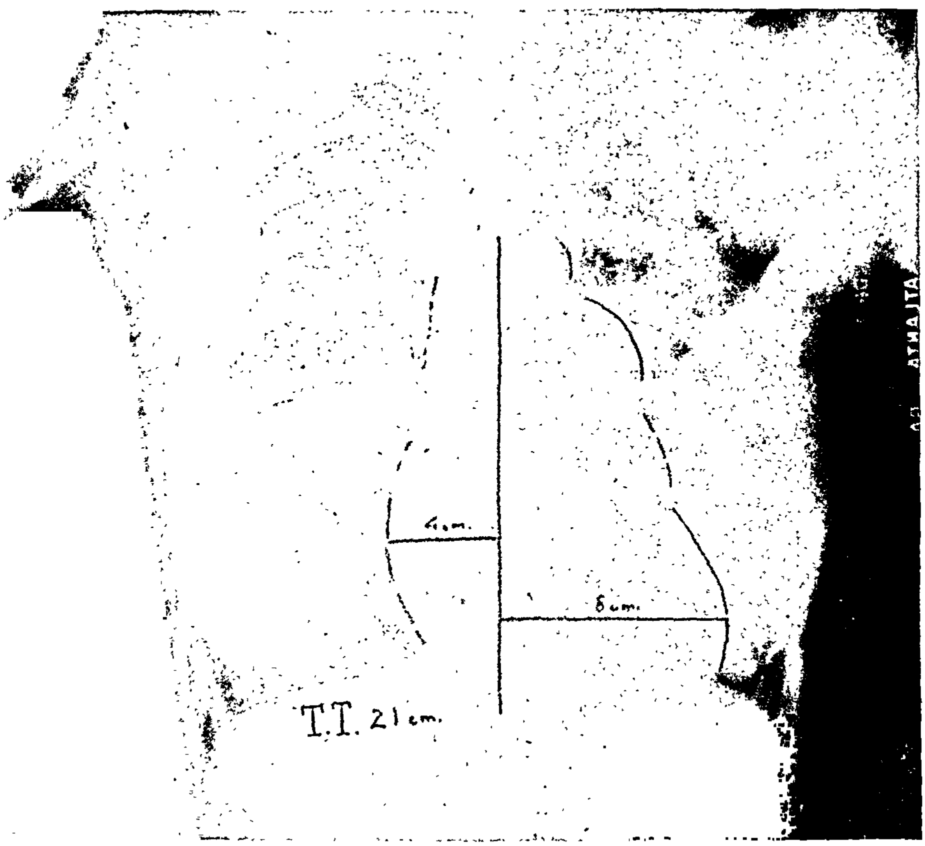

Fig. 1.—Teleoroentgenogram of B. T., in March, 1931. Note the prominence of the pulmonary conus and artery, the increase in the density of the hilar vessels, and the enlargement to the right. The aorta and the tip of the left atrium can also be made out.

The teleoroentgenogram is shown in Fig. 1. Fluoroscopically, the pulmonary trunk could be seen to expand during systole, and alterations in the density of the hilar vessels, particularly on the right, were observed with the heart beat. The electrocardiogram exhibited only right axis deviation.

Diagnosis.—Although signs of mitral stenosis were evident, congenital mitral stenosis is rare, and the roentgenologic appearance was not typical. B. T.'s symptoms dated back to infancy, and the diagnosis of congenital heart disease therefore seemed warranted.

Course.—She spent most of her waking hours reading, day-dreaming, and writing verse. However, she continued to have frequent and ever more excruciating attacks of anginal pain; she realized that she might die in any one of them, and wished as much as an intensely devout girl could that she might be released from her suffering.

She spent May 8, 9, and 10, 1936, at a religious revival which caused her great emotional excitement; this was climaxed when her uncle, who was a drunkard, promised to reform. After walking two blocks from the streetcar on her return home the following day, she collapsed and began to cough up frothy, bloody sputum. The heart rate ranged from 140 to 150 until her death ten hours later.

Necropsy.—The general outline of the heart was that of an inverted keystone, as shown in the roentgenogram. The external diameter of the pulmonary artery was 3 cm. There was no communication between the atria or between the ventricles. The ductus arteriosus was closed. The average thickness of the wall of each ventricle was 12 mm. The tricuspid valve was normal, measuring 8 cm. The inner circumference of the pulmonic valve was 8 cm. The pulmonary artery appeared normal, except for its dilatation, and so did the proximal parts of its main branches. The mitral valve was deep, tremendously thickened, and stenosed; its orifice measured about 6 by 8 mm. The inner circumference of the aortic valve was 5.5 cm. The aorta looked normal, and there was no anomaly in the origin of the coronary arteries or of the great vessels. Grossly the heart muscle seemed healthy. The lungs were almost solid with edema.

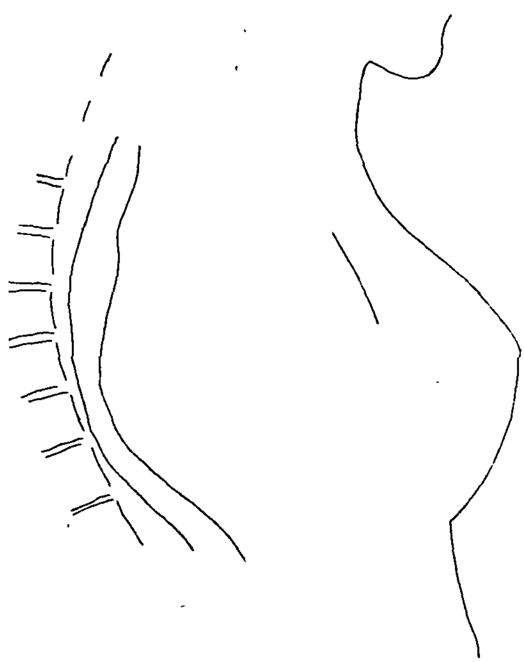

Fig. 2.—Tracing of the lateral teleoroentgenogram of B. T. The displacement of the esophagus, which was visualized with barium, reveals the degree of dilatation of the left atrium.

CASE 2.—R. D., a newspaperman, aged 36, was first examined by me on March 15, 1933. In 1915, after two weeks of rheumatic fever, he resumed a very active life. During the course of an examination for life insurance, in 1920, a heart murmur was discovered. In 1928 he began to notice that playing eighteen holes of golf exhausted him. At about the same time he experienced an excruciating pain which began in the left humerus and radiated back to the precordium and down to the xiphoid, and was associated with dyspnea, palpitation, and, at times, tachycardia. These attacks, which lasted perhaps four minutes, would terrify him. He had four or five similar attacks from 1928 to 1930. Christmas night, 1932, he experienced his first attack of nocturnal orthopnea. By that time his endurance had decreased to such an extent that he had had to give up golf, and walking two blocks uphill would tire him.

Examination.—In March, 1933, the heart was slightly enlarged to the left, but no thrill was made out. At the apex, a soft diastolic murmur, which merged into a presystolic murmur, and a rough systolic murmur were noted. The pulmonic second sound was markedly accentuated. The blood pressure was 104/74; the pulse rate was 92. The teleoroentgenogram revealed the typical mitral configuration, without great enlargement.

Diagnosis.—Aside from the history, the physical signs justified the diagnosis of rheumatic heart disease, with mitral stenosis. The anginal attacks were attributed to rheumatic changes, such as those described by Karsner and Bayless,[14] in the coronary arteries. In view of the steady lessening of the cardiac reserve during the preceding five years, a rather grave prognosis was given.

Fig. 3.—Post-mortem anteroposterior roentgenogram of the heart of R. D., showing the calcification of the mitral valve.

Course.—He continued to have severe attacks of pain, usually following exertion. In none which I observed did the heart rate exceed 120. Severe congestive failure had developed by September, 1936. After this, in spite of staying in bed most of the time, with rigid restriction of fluid and salt intake, and frequent injections of salyrgan, his condition grew steadily worse.

In the summer of 1938 there were several paroxysms of tachycardia, with a heart rate of about 180. These attacks were not associated with pain, although he expected to die in each one. Each of these subsided after an injection of 5 grains of soluble phenobarbital. He had several alarming pulmonary emboli, but only two attacks of angina, in 1938. The abdomen was tapped, and 8,000 to 10,000 c.c. of fluid removed, in June, July, and August, and Southey tubes were used from Aug. 11 until his death, a week later.

The systolic blood pressure was usually from 90 to 100, with a pulse pressure of 20, or less; the best reading was 124/88, and the poorest, a few weeks before death, 84/76.

The electrocardiograms were of interest only in that they showed a gradual decrease in the amplitude of the QRS complexes. Successive teleoroentgenograms showed a gradual increase in the size of the heart. Before his death, marked curvature of the nails had developed.

Necropsy.—The body was waterlogged. Several pulmonary infarcts, in various stages of resolution, were observed. The heart weighed 547 Gm. The mitral valve was thickened, calcified, and stenosed; the opening measured approximately 6 by 8 mm. The coronary arteries were normal. The left ventricle was scarred and relatively atrophic. The pulmonary arteries appeared to be normal.

Microscopic Examination.—Microscopic examination by Dr. Francis P. Parker revealed extensive scarring of the myocardium, but no coronary lesions. The pulmonary arteries were normal.

Comment.—It is worthy of note that auricular fibrillation was never detected in this patient; even during the paroxysms of tachycardia, in the last three months of his life, the heart beat was regular.

DISCUSSION

Both of these patients with mitral stenosis suffered, for a number of years, frequent, severe attacks of classical angina pectoris, including the sense of impending dissolution.

In spite of the difference in sex, age, social position, and educational advantages, these two patients had many things in common. Each had a family history of psychic instability, and each was a thin, highstrung, highly emotional, at times hysterical, person.

The first patient never enjoyed much cardiac reserve, but she never exhibited frank signs of congestive failure until the terminal pulmonary edema. The second patient had his first signs of grave myocardial insufficiency eight years after the onset of minor symptoms, and twenty-one years after the attack of rheumatic fever.

Each was subject to attacks of paroxysmal tachycardia. During the course of an examination the girl's heart rate would suddenly increase to 140 or 150, but she would have no pain. The man might suffer extreme pain in the left arm when his heart rate was not more than 120, but during three of his paroxysms, when the heart rate was 180, he was observed to have pronounced precordial oppression, dyspnea, and fear of impending death, although true anginal pain was conspicuously absent. It is quite possible, however, that the anginal crises were often precipitated by tachycardia.

In the first case, perhaps the most serious obstruction was in the pulmonary circulation and was caused by a primary sclerosis of the lesser system such as Posselt[15] has described. It is possible that the primary lesion was congenital mitral stenosis, and that this obstruction raised the pressure in the pulmonary arteries to such an extent that eventually they underwent secondary sclerotic changes. In the second case there was no serious disease of the pulmonary artery or its branches. The mitral valve was calcified, and there was extensive fibrosis of the myo-

cardium. In both cases the coronary arteries were grossly normal, and in one of them they were normal microscopically, also.

It would appear, then, that the anginal seizures in both cases were caused by the fact that the left ventricle did not receive blood fast enough to enable it to sustain in the proximal aorta a pressure adequate to fill the coronary arteries when these arteries were called on to meet extra demands.

It is suggested that, if more attention were paid to symptomatology in cases of rheumatic heart disease, angina pectoris would be reported more often.

SUMMARY

Two cases of angina pectoris which was associated with, and probably caused by, verified mitral stenosis are reported.

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TERMINAL CARDIAC MECHANISM IN CORONARY ARTERY DISEASE*

Report of Two Cases

Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla.

IN NOVEMBER, 1938, Grieco and Schwartz[1] demonstrated that ventricular standstill may be the cause of death after acute coronary artery thrombosis. They did not observe ventricular fibrillation following the ventricular tachycardia which preceded cardiac death. In June, 1939, F. Janney Smith[2] reported, from this clinic, a case in which ventricular fibrillation occurred after acute coronary artery thrombosis. It has been our singular experience to observe electrocardiographically, during one afternoon, the terminal cardiac mechanism in two instances of sudden death from coronary artery disease. One of these deaths was shown, at autopsy, to have been caused by marked coronary artery sclerosis (the patient had had angina pectoris). The other was undoubtedly the result of infarction of the anterior wall of the heart; it occurred on the tenth day following the coronary occlusion.

CASE REPORTS

Case 1.—A. J. A. (No. 79986), a white man, 46 years old, was first seen in June, 1926. On subsequent occasions, in the hospital and outpatient department, he had been treated for a number of minor complaints. No serious illness was noted until Aug. 2, 1939, when he stated that for several weeks he had had severe, aching pain in both shoulders and down both arms. The distress was periodic and would last only a few minutes. It was present only during exertion, and was relieved promptly by rest. It was most likely to occur after meals. There had been no substernal or precordial distress.

On Aug. 11, 1939, abut 3:00 p.m., the patient made one of his regularly scheduled visits to the outpatient department. He had been feeling well and had noted no distress or discomfort that day. In the lobby of the hospital he collapsed, became unconscious and cyanotic, and shortly vomited. He was brought to the cardiac clinic, where he recovered for a few moments and indicated that he was having crushing substernal pain. Concentrated glucose solution (100 c.c. of 20 per cent), with 3.5 grains (0.25 gram) of aminophyllin, was administered intravenously. He soon lapsed into complete coma. The ashen cyanosis increased. The cardiac rate was 54, and the beating was regular. The blood pressure could not be obtained, and the peripheral pulse was imperceptible. He was sweating profusely. An electrocardiogram was obtained. He was given 0.5 c.c. of adrenalin subcutaneously, and heat was applied externally. A pronounced protodiastolic gallop rhythm was present, together with irregularly occurring extrasystoles. The electrocardiograph was again connected. At about 3:15 p.m. a severe clonic convulsion occurred, and respirations ceased. The heart sounds could not be heard, and it was felt that the patient was dead. Artificial respiration was applied, and 1 c.c. of adrenalin was injected into the heart. No further evidence of life appeared except in the electrocardiogram (Fig. 1).

*From the Department of Medicine, Henry Ford Hospital.

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After 3:15 P.M., when, from the clinical standpoint, the patient was dead, the record first showed an almost regular heartbeat, at a rate of approximately 150, and complexes which varied slightly in contour. Three minutes later the complexes were smaller and varied more. At 3:20 and 3:21 there were prominent, rounded waves which occurred at a rate of 72; they were preceded and followed by very small deflections. At 3:22, there was, for a time, no evidence of ventricular activity, for

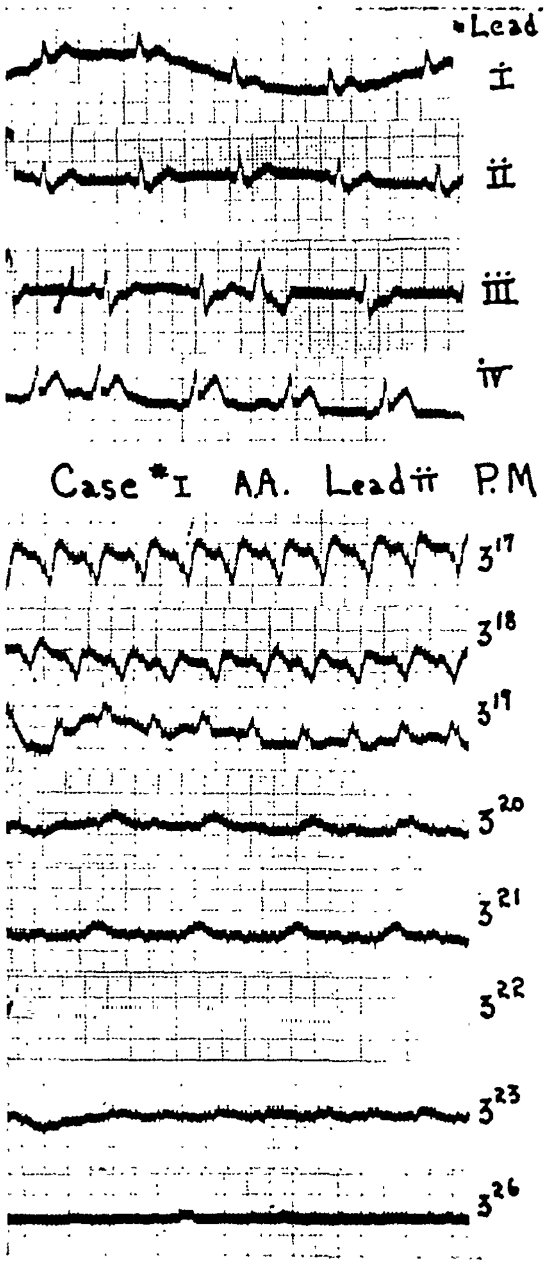

Fig. 1.

the small deflections which occurred at a rate of less than sixty a minute may have been entirely of auricular origin. With the resumption of ventricular activity, at 3:23, although the voltage was small, there continued to be a recurring similarity in the form of the complexes. The last portion of the record showed a further decrease in the amplitude of the deflections.

The autopsy was performed by Dr. G. B. Kerr. The left anterior coronary artery was tortuous and thickened, and the lumen was almost obliterated in several places by confluent atherosclerotic plaques. No fresh thrombus could be seen. The right coronary artery showed only an occasional patch of atherosclerosis. No area of myocardial infarction could be demonstrated, either grossly or by histologic section.

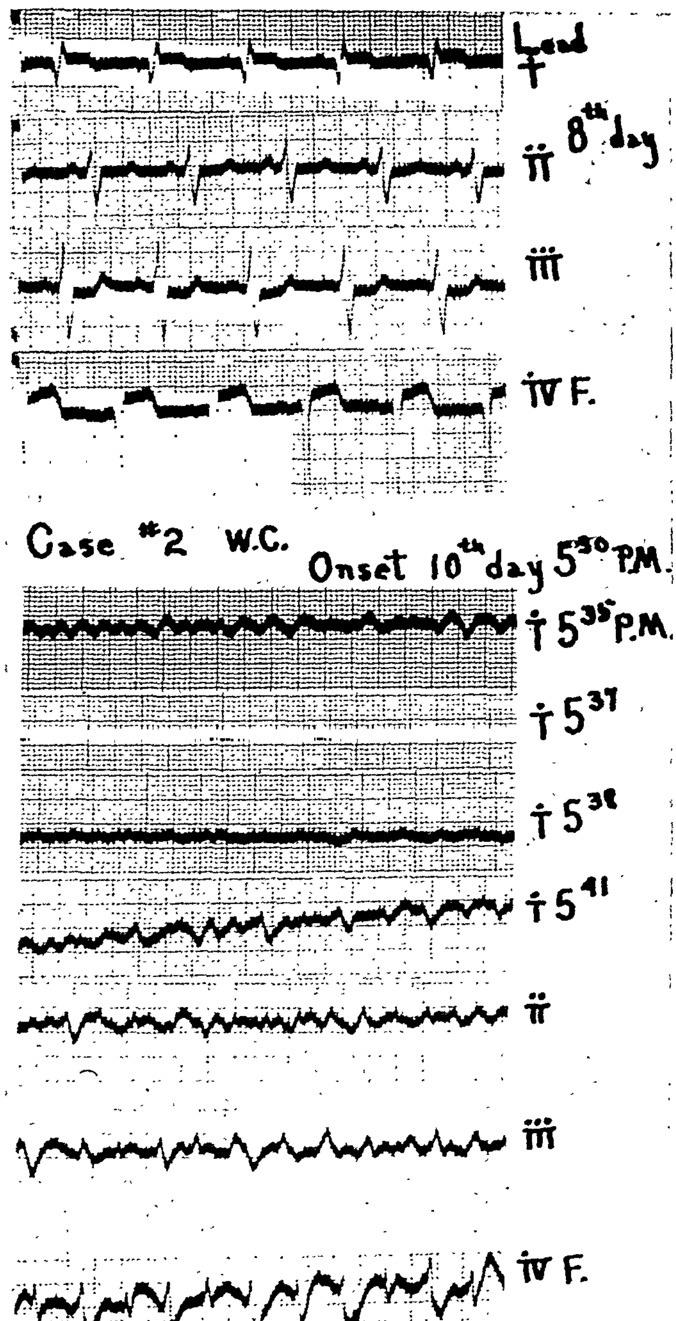

Fig. 2.

Department of Reviews and Abstracts

Selected Abstracts

Hoyos, Jorge Meneses, and Palacios, Hector Caraza: Experimental Studies on the Action of Ascorbic Acid on the Heart. An. Inst. de Biologia **10:** 173, 1939.

A solution of ascorbic acid, 1:1,000, produced increased amplitude and frequency of the heart of the turtle and the frog.

Ascorbic acid has no action upon the isolated turtle's heart other than perhaps that of producing a slight increase in the amplitude of the auricular beats.

In experimental scurvy there is a diminished voltage in the electrocardiogram; cure results in return to normal voltage.

The voltage of the normal human electrocardiogram can be increased by intravenous injection of small doses of ascorbic acid. The same can be done with stimulating doses in the rabbit. Toxic doses cause a diminution of voltage.

The effect appears to be directly on the ventricle.

JENSEN.

Maldonado-Allende, Ignacio, Orias, Oscar, and Segura, Angel S.: Attempts to Register Cardiac Sounds During Experimental Ventricular Fibrillation. Actas y Trabajos del VI Congreso Nacional de Medicina, Cordoba, vol. I, 1939.

Twenty-two dogs were used for the experiments. Their hearts were exposed and electrocardiograms and audiograms of the regular action were obtained. The ventricles were then made to fibrillate, and the fibrillation was recorded by electrocardiograms. The audiogram showed vibrations of a frequency which classed them as sound waves. The findings, however, were not as constant as the authors could wish, and the amplitude of the waves varied from moment to moment. In some cases in which the auricles continued to beat regularly, the waves indicating auricular activity continued as before. When they also fibrillated, they gave rise to waves similar to those produced by the ventricles. It is suggested that such researches may throw some light on the origin of the heart sounds.

JENSEN.

Bloomfield, Arthur L.: Dysphagia With Disorders of the Heart and Great Vessels. Am. J. M. Sc. **200:** 289, 1940.

Dysphagia may occur in connection with the following disorders of the heart and aorta: dilated left auricle, pericarditis, saccular aneurysm, dissecting aneurysm, and anomalous aortic arch.

While pressure on the esophagus is common with all of these conditions, clinical dysphagia occurs very rarely except with saccular aneurysm and anomalous aortic arch.

Difficulty in swallowing in a patient with pericarditis suggests a large effusion.

Marked dysphagia with aneurysm suggests a false sac or huge lesion with threatened rupture.

Dysphagia in a supposed case of coronary occlusion should arouse suspicion of dissecting aneurysm.

The literature dealing with the above conditions is reviewed, and a case of dysphagia associated with compression of the esophagus by an enlarged left auricle is reported.

AUTHOR.

Coelho, Eduardo, deCosta, Filipe, and deOliveira, Artur: Novocaine Infiltration of the Stellate Ganglion in Angina Pectoris. Impressa Medica. 5: 3, 1939.

The authors submitted patients with angina pectoris to exercise tolerance tests (stair climbing). They studied the effect both on the pain and on the electrocardiogram. In 70 per cent of their cases there were electrocardiographic changes following effort; these changes did not necessarily coincide with the onset of pain. Nine patients had bilateral injections of novocain into the stellate ganglion; seven had it in the left side only. In each case the injection was followed by Claude-Bernard-Horner syndrome. A control series of normal persons were similarly injected, and their electrocardiographic response to effort was tested before and after injection. Neither effort nor injection had any effect on the electrocardiogram. In the patients with angina pectoris the blocking of the ganglion prevented the pain, but it did not change the electrocardiographic response. The authors concluded that the operation only interrupted the painful sensations, but had no effect on the coronary circulation. Believing that angina pectoris is caused by coronary vasoconstriction, they assumed that the operation did not interfere with the vasoconstrictors. The operation did not delay the onset of fatigue which formerly had stopped the patients, nor did it enable any of them to climb more steps.

JENSEN.

Sodeman, William A., and Engelhardt, Hugo T.: A QRS Pattern of Diagnostic Value in the Electrocardiogram. Am. J. M. Sc. 200: 337, 1940.

A QRS pattern is described which has been found to occur in tracings from patients with heart disease in the absence of any other electrocardiographic evidence of heart disease. It promises to be of value in electrocardiographic interpretation.

AUTHORS.

Puddu, Vittorio: On the Duration of Cardiac Systole During Hypocalcemia. Boll. e atti della R. Academia medica di Roma. 64: 131, 1938.

In two cases of hypoparathyroid hypocalcemia the author found that systole as measured by the electrocardiogram was prolonged as compared with normal. This difference was not demonstrable with the sphymograph.

JENSEN.

Mussafia, A., and Puddu, V.: Electrocardiographic Researches With Multiple Thoracic Leads. Boll. e atti della R. Acedemia medica di Roma 64: 277, 1938.

Authors examined twenty-eight subjects, with the exploring electrode on various points of the precordium and with the indifferent electrode always in the left leg.

Four positions were selected: the fourth left interspace near the sternum, the apex beat, a point midway between the two at the level of the apex beat in the anterior axillary line, and the midaxillary line.

They conclude that the electrocardiogram depends on the size of the heart and its position within the chest. It is determined by the potential of the adjoining part of the heart. The less the distance of the heart from the electrode, that is, the closer the heart is to the chest wall, the more circumscribed is the surface of the heart which affects the electrode. These two statements are confirmed by numerous other researches.

JENSEN.

Mussafia, A., and Puddu, V.: Results of Two Precordial Leads. Cuore e circolaz. 23: 281, 1939.

In 500 tracings on 400 patients, two precordial leads were compared, one with the exploring electrode on the fourth intercostal space at the parasternal line (CF_2), and the other with the exploring electrode at the apex lead (IV F). In both, the indifferent electrode was on the left foot.

Lead IV F is more specific and more sensible than CF_2, when the general cardiac state is considered. However, in some patients with heart disease, CF_2 alone was affected; especially in some cases of myocardial infarctions was the electrocardiographic change present only in CF_2.

The authors recommend the use of both precordial leads together, at least when coronary thrombosis is suspected.

JENSEN.

Coelho, Eduardo, and deOliveira, Artur: Tachycardia and Paroxymal Ventricular Fibrillation in Infarction of the Myocardium. Cardiologia 3: 169, 1939.

Three case reports of ventricular tachycardia and one of ventricular fibrillation following cardiac infarction are given. The attacks were of unusually long duration and occurred in younger patients (aged 45, 40, and 38 years). The article is accompanied by numerous electrocardiogram tracings.

AUTHORS.

Davis, John S., Jr.: Diagnosis and Treatment of Gonorrheal Septicemia and Gonorrheal Endocarditis. Arch. Int. Med. 66: 418, 1940.

Gonorrheal endocarditis is a fairly common disease. The diagnosis can and should be made early so that proper treatment may be instituted. Since a positive blood culture is frequently hard to obtain and is not the only diagnostic criterion, it is not absolutely necessary, and it may be dangerous to delay the diagnosis for lack of this one determination. The high percentage of diagnoses made at autopsy bears mute testimony to this. The high mortality should, in the future, be curtailed and the majority of the patients should recover.

AUTHOR.

Rosenberg, David H.: Bacterial Endocarditis and Syphilis of the Aortic Valve. Arch. Int. Med. 66: 441, 1940.

The literature dealing with bacterial endocarditis and syphilitic valvular disease is critically reviewed, and the reported cases are grouped categorically as proved, doubtful, and unproved.

Since Libman first directed attention to the infrequent concurrence of these diseases, only ten proved cases have been reported. To these, the records of seven more instances are added, making a total of seventeen proved cases. Of the remaining cases in the literature, four are regarded as doubtful, and in twenty-nine the existence of syphilitic aortic valvular disease remains unproved.

Based on the available data, a study of the incidence is made, and the suggestions offered for the interpretation of the rarity of this combination are discussed. Attention is drawn to the diagnostic difficulties and to the limitations of a positive Wassermann reaction.

Contrary to the opinions expressed in current literature, it is apparent from this study that bacterial endocarditis associated with syphilitic aortitis per se (without involvement of the aortic cusps or commissures) is not of rare occurrence.

With greater interest directed to the clinical and anatomic recognition of bacterial endocarditis superimposed on syphilitic valvular deformities, it is likely that their coexistence may be observed more frequently than heretofore.

AUTHOR.

Gauld, Ross L., and Read, Frances E. M.: Studies in Rheumatic Disease. V. The Age at Onset of Primary Rheumatic Attack. J. Clin. Investigation 19: 729, 1940.

Various defects in published data relative to the age selection of rheumatic disease are discussed, and the results of a study on this subject, in which every effort was made to eliminate these errors, are presented.

The group for study was a generation of families of ninety-six consecutive patients admitted to the Cardiac Clinic of the Harriet Lane Home because of rheumatic disease, and it consisted of parents, uncles, and aunts of these patients (index cases).

The accuracy of the data and various possible errors in the histories are recognized and discussed.

The age at onset of 115 cases of rheumatic disease occurring in the generation was found to fall most frequently between the ages of 5 and 14 years, and 25 and 34 years.

The relative risk of developing the disease was determined by dividing the number of onsets at each age by the person-years at risk for the corresponding age to obtain an annual incidence rate. This risk was found to be greatest between the ages of 5 and 14 years and 25 and 34 years.

AUTHORS.

Coelho, Eduardo, and deOliveira, Artur: Syphilis of the Interventricular Septum and Ventricular Tachycardia; Syphilis of the Pulmonary Artery. Arch. d. mal. du Coeur 32: 17, 1939.

This report of a gumma in the interventricular septum is the second case of the kind reported in the literature. The patient, aged 24 years, died from heart failure and A-V block and defective intraventricular conduction. At autopsy there were shown syphilitic changes in the pulmonic valves and in the pulmonic artery. There were also gummas in the interventricular septum.

This case is of exceptional interest.

JENSEN.

Bruck, Max: Is There a Physiologic Hypertonia of the Aged? Cardiologia 4: 165, 1940.

The author examines the question whether there is a physiologic arterial hypertension in old age and whether the increased blood pressure in old age is a sign of disease.

The blood pressure levels, studied in healthy students of athletics, fluctuate according to Gaus' curve.

The figures in older people do not conform to the Gaus' curve and there is no evidence for increased physiologic fluctuations. The observations can be interpreted as a mixture of the normal curve with pathologic figures; thus, it is impossible to deduce a physiologic increase of the arterial blood pressure in old age from these observations.

There is no evidence for a physiologic increase in arterial pressure in old age. There is evidence for the view that the pressure remains stationary or may even decrease.

The probability for the fluctuations of arterial pressure in normals is calculated. The probability is small that a pressure of 150 mm. Hg falls within the range of the normal.

AUTHOR.

de Navasquez, S., Forbes, J. R., and Holling, H. E.: Right Ventricular Hypertrophy of Unknown Origin: So-called Pulmonary Hypertension. Brit. Heart J. 2: 177, 1940.

Three cases of severe right ventricular hypertrophy of unknown origin have been described.

The usually accepted causes of such hypertrophy due to disease of the heart and lungs have been excluded.

The clinical and pathologic changes have been described and discussed.

It is suggested that the term "idiopathic right ventricular hypertrophy" should in future replace "primary pulmonary arteriosclerosis" or "hypertension," which have no foundation in fact.

AUTHORS.

East, Terence: Pulmonary Hypertension. Brit. Heart J. 2: 189, 1940.

Three cases are described in which failure of a conspicuously hypertrophied right ventricle took place. At autopsy no satisfactory cause for this hypertrophy could be found.

They present a clinical picture which should be fairly easily recognizable during life.

1. Enlargement of the right ventricle, with the characteristic electrocardiogram.
2. Enlargement of the pulmonary artery, confirmed by the skiagram.
3. A loud pulmonary second sound suggesting a high pressure in it.
4. Intractable and progressive failure of the right ventricle, with the maintenance of normal rhythm, dyspnea of any severity being absent.
5. A normal appearance of the left auricle.
6. An absence of valvular defects, congenital or acquired, or of patent septa. (Patent interauricular septum might be difficult to exclude.)
7. An absence of pulmonary disease.
8. The absence of evidence of syphilis.

It is suggested that a condition of idiopathic or essential pulmonary hypertension may exist as a cause for those findings.

AUTHOR.

Armstrong, T. G.: Failure of the Right Ventricle. Brit. Heart J. 2: 201, 1940.

It is suggested, that the duration of the failure and its unremitting nature in this case were due to the right ventricle failing alone. The unusual pathologic findings, the cardiac "cirrhosis" of the liver, and the chronic indurative changes in the peritoneum, were probably an expression of the extreme chronicity of the disease, and are strictly comparable with the findings in constrictive pericarditis.

AUTHOR.

Schiappoli, Franco: On the Significance of Venous Pressure Registered by Clinical Methods. IV. Modification in Normal Subjects Following Reflex Stimulation, Thermal and Mechanical. Cardiologia 4: 214, 1940.

Changes of venous pressure following thermal and mechanical stimulation and after pressure on the carotid sinus and the eyeball were studied. Changes were observed which were independent of variations of arterial pressure with regard to duration, extent, and direction. Considerable changes were observed following stimulation which produced definite parasympathetic excitation.

The determining factor influencing venous pressure is the tone of the veins. Changes in venous pressure can be produced only by reflexogenous modifications.

AUTHOR.

Robinson, S. C., and Brucer, Marshall: Body Build and Hypertension. Arch. Int. Med. 66: 393, 1940.

A review of the literature shows that no rigidly controlled statistical study on a sufficiently large series has conclusively established a positive correlation between blood pressure and body build. Some writers contend that no correlation whatsoever exists.

In this study of blood pressure and body build, made on 3,658 persons, an index derived from dividing the chest circumference by the standing height was used as a ratio of width to height to distinguish the narrow linear type of persons from the broad lateral type.

Among 1,861 men and 1,797 women, 17 per cent of the men and 31 per cent of the women were of the narrow-chested, linear type of build, and 12 per cent of both men and women were of the broad-chested, lateral build.

Observations lead both to the general conclusion that a positive correlation between body build and blood pressure does exist and to the following specific conclusions:

In both men and women there is an increase in the average build—chest-to-height ratio—with an increase in age. This increase in the adult is greatest before the age of 50 years; after this age there is a tendency for the average build to decrease.

Men and women of lateral, or broad, build show a marked tendency to hypertension. The mean, median, and modal systolic and diastolic blood pressures increase with an increase in chest-height ratio.

The lateral, broad-chested type of man has more than four times the expectancy of development of diastolic hypertension as has the man of linear, or slender, build. The women of lateral build have almost eleven times the expectancy of development of systolic hypertension and eight times the expectancy of diastolic hypertension as have the women of linear build.

The men and women of lateral build have only about one-half the expectancy of a low systolic or diastolic pressure as have men and women of the linear build.

In any random group of men of lateral build, high systolic and diastolic pressures occur three times as often as low pressures. In any random group of women of lateral build, the ratio of high systolic pressure to low systolic pressure is 5:1, and the ratio of high diastolic pressure to low diastolic pressure is 4:1.

In any random group of men of linear build, the ratio of low systolic pressure to high systolic pressure is 3:1, and the ratio of low diastolic pressure to high diastolic pressure is 5:1. In the group of slender women the ratio of low to high systolic or diastolic pressures is 4:1.

In any random group of persons with systolic hypertension the ratio of lateral to linear builds will be: men, 4:1; women, 11:1. In any random group of persons with diastolic hypertension the ratio of lateral to linear builds will be: men, 7:1; women: 8:6.

In any random group of persons with low systolic pressures the ratio of linear to lateral builds for both men and women will be greater than 2:1. In those with low diastolic pressure the corresponding ratio for men will be greater than 2:1, and for women, almost 2:1.

The relation between lateral build and hypertension and between linear build and low blood pressure is found in all age groups.

The incidence of high pressures increases and that of low pressures decreases with age in men of lateral build. In those of linear build the incidence of high pressure is constant up to the seventh decade; the incidence of low pressure is constant throughout life.

The incidence of high pressures increases with age more markedly among women of lateral build than among those of linear build, and at every age the incidence of low pressure is greatest among the women of linear build.

AUTHORS.

Williams, J. R., Jr., Grollman, Arthur, and Harrison, T. R.: The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract. Am. J. Physiol. 130: 496, 1940.

A series of eighteen hypertensive dogs were treated with renal extracts. The blood pressure of these animals was reduced appreciably, normal values being attained in some cases. Severe untoward symptoms accompanied this reduction in many cases. The bearing of these findings on certain aspects of the problem of renal hypertension has been discussed.

AUTHORS.

Wakerlin, G. E., and Gaines, Walter: The Effect of Various Agents on the Blood Pressure of Renal Hypertensive Dogs. Am. J. Physiol. 130: 568, 1940.

Estrone, testosterone, and extracts of liver, pancreas, and garlic and parsley had no significant effect on the blood pressures of renal ischemic hypertensive dogs.

Temporarily, dog renin slightly but significantly increased the blood pressures of renal hypertensive and normal dogs.

Fresh hog kidney, adrenal cortical extract, whole pituitary extract, and pituitrin were without effect on the blood pressure in experimental renal hypertension in dogs.

Distemper lowered the blood pressures of renal hypertensive dogs but extensive cellulitis was without effect.

The growing evidence of similarity between experimental renal ischemic hypertension in the dog and essential hypertension in man is further substantiated.

AUTHORS.

Maldonado-Allende, Ignacio: Influence of Tobacco on Arterial Hypertension. Actas y Trabajos del VI Congreso Nacional de Medicina, Cordoba, Vol. II, 1939.

The author analyzed the effect of tobacco smoke on twenty-four patients with arterial hypertension, who were smokers and nonsmokers; he tested the effect on the heart rate, the blood pressure, and the electrocardiogram.

Heart rate and blood pressure showed no significant changes. The electrocardiogram showed transient changes in the T waves in some or in all leads, in a high percentage of cases. These changes occurred more frequently in patients with hypertension. The changes are explained by (1) direct toxic effect on the myocardium, (2) indirect toxic effect via the nervous system, (3) production of chemical changes in the blood, slight, but still sufficient to influence cardiac nutrition, (4) constriction of the coronary arteries by the tobacco.

It is thought that this effect regularly produced on the smoker's heart may eventually result in permanent cardiac damage.

JENSEN.

Scaffidi, Vittorio, Jr., and Positano, Giuseppe: On the Significance of Venous Pressure Registered by Clinical Methods. V. On the Existence of Reflex Venous Zone in the Region of the Superior Vena Cava. Cardiologia 4: 235, 1940.

Mechanical stimulations of the preauricular region of the inferior vena cava in dogs with closed chest produced hypertension in these zones; stimulations of the superior vena cava lower the pressure in the region of the superior vena cava. These fluctuations of venous pressure are due to reflexes which regulate the venous circulation.

AUTHORS.

Keil, Harry: Dermatomyositis and Systemic Lupus Erythematosus. I. A Clinical Report of "Transitional" Cases, With a Consideration of Lead as a Possible Etiologic Factor. Arch. Int. Med. 66: 109, 1940.

The protocols of five cases are recorded in detail in order to depict the varied manifestations of dermatomyositis as well as to illustrate what may be called a condition "transitional" between that disease and systemic lupus erythematosus. Additional examples of this condition are mentioned only in connection with the elaboration or substantiation of certain points. A preliminary attempt is made to clear the ground for a more detailed consideration of the similarities and the differences in the clinicopathologic features exhibited by each of these diseases in their typical forms.

Two instances of dermatomyositis are described, one very briefly, in which there appeared suggestive evidence that the factor of lead played an important part in the evolution of the clinical picture. These cases are not isolated and are considered in relation to the data indicating that this heavy metal is a vascular poison, especially in certain susceptible persons. These data are carefully reviewed, notably because there is a tendency on the part of observers to attribute various disease to lead absorption; whenever such views are advanced, critical investigators have, with considerable justification, refused credence to them. Moreover, the cases under my observation did not present the classic evidence of plumbism. Nevertheless, it is suggested that lead may exert a deleterious effect on the blood vessels in especially susceptible persons with a presumably unstable vascular system, and in such persons "vascular disease may be and remain the solitary sign of lead poisoning." The connection between this heavy metal and vascular disease is regarded as probable, even though specific or pathognomonic lesions are not produced. The evidence compiled in this paper cannot be summarily dismissed without further investigation of the problem, which is admittedly difficult.

AUTHOR.

Keil, Harry: Dermatomyositis and Systemic Lupus Erythematosus. II. A Comparative Study of the Essential Clinicopathologic Features. Arch. Int. Med. 66: 339, 1940.

This study is concerned with a comparative analysis of the essential clinicopathologic features presented by systemic lupus erythematosus and dermatomyositis. Among the clinical phenomena encountered in both diseases are fever, pains generally regarded as articular, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leucopenia, tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement, and renal disease. At times both diseases may also run an afebrile course, and the clinical picture may occasionally be dominated by what may be called the sequelae of these conditions. Despite these similarities and the occasional overlapping of features, the average typical example of each disease runs a fairly distinctive course. The main body of the paper is devoted to an analysis of the differences in the clinicopathologic attributes. These are studied under the following headings: (1) age, sex, and seasonal incidence, (2) cutaneous lesions, (3) disease in the muscles, (4) involvement of subcutaneous tissue, (5) articular involvement, (6) renal disease, (7) ophthalmoscopic observations, (8) cardiac involvement, (9) disease in the serous membranes, (10) anomalies of the lymph nodes, (11) involvement of the spleen, (12) disease in the liver, and (13) involvement of the brain. Certain laboratory data are also compared. Likewise, differences in the prognosis are briefly discussed. Finally, the pathologic data thus far available are subjected to a critical examination with respect to their significance for diagnosis, and an effort is made to expose some of the many problems encountered in the evaluation of such observations.

AUTHOR.

Bowers, James M.: Arteritis of the Temporal Vessels. Arch. Int. Med. 66: 384, 1940.

Report of a case of inflammation of the temporal arteries is presented. For a considerable period before diagnosis the associated headache was attributed to severe arterial hypertension. Undoubtedly, the occipital arteries were involved in a similar inflammatory process at the same time. Nine months after the subsidence of signs and symptoms, the patient suffered a cerebral vascular mishap, which probably was due to arteritis of the cerebral vessels, of the same nature. Interruption of the pain pathway of the sympathetic nervous system after resection of an arterial segment and injection of vitamin B_1 produced relief from pain. Many points in favor of designation of this condition as a separate entity of arteritis, especially of its distinction from periarteritis nodosa, may be found in the reports of the sixteen cases now on record.

AUTHOR.

Patek, Arthur J., Jr., Post, Joseph, and Victor, Joseph C.: The Vascular "Spider" Associated With Cirrhosis of the Liver. Am. J. M. Sc. 200: 341, 1940.

The vascular spider, associated with disease of the liver, has the physiologic characteristics of an artery. This has been demonstrated by studies on direction of blood flow, pulsations, contractility, intravascular pressure, nad pharmacologic reactions.

In serial sections, the histologic characteristics of two lesions are those of an artery and its arteriolar branches. In five others they resemble, in a magnified form, the arterial segment of an arteriovenous anastomosis (glomus). However, the branches of these vessels are continued into capillaries and are not directed into veins.

AUTHORS.

Lippincott, Stuart W.: Abdominal Aortic Mycotic Dissecting Aneurysm. Canad. M. A. J. 43: 115, 1940.

This is a case report of an abdominal aortic aneurysm in which the gross examination did not reveal the nature of the process. Detailed microscopic studies showed both arteriosclerosis and syphilis although they were not the underlying factors in the dissecting aneurysm. The formation of this resulted from a septic medial necrosis. There was a complicating infection in the ear and the right knee joint, containing β-hemolytic streptococci. These organisms were responsible for the production of the aortitis, with medial necrosis, intimal rupture, and formation of this rare form of dissecting aneurysm.

MCCULLOCH.

Porter, William B., and Vaughan, Edwin W.: Coronary Embolism: A Complication of Syphilitic Aortitis. Am. J. M. Sc. 200: 184, 1940.

Thirty cases of coronary embolism are analyzed as to age, sex, source of embolus, branch of the coronary artery occluded, and type of death. Three new cases of coronary embolism are reported, all of which occurred in colored males. Syphilitic aortitis was the indirect source of the embolus in each case.

AUTHORS.

Weiss, Soma, Kinney, Thomas D., and Maher, Mary M.: Dissecting Aneurysm of the Aorta With Experimental Atherosclerosis. Am. J. M. Sc. 200: 192, 1940.

Three cases of healed and functioning dissecting aneurysm are reported. Endothelium and atherosclerosis developed over the internal surface of the new aortic

channel. The *atherosclerosis of the* dissected aortic wall was pronounced in one of *the* cases *and mild* in two. In none of the cases did the existence of a double-channeled aorta contribute to the death of the patient.

In a 73-year-old female, with a healed dissecting aneurysm, the roentgen-ray picture revealed a double shadow corresponding to the double-channeled aorta. The surface of the new aortic channel was covered with numerous atherosclerotic plaques and endothelial islands.

In Case 2 endothelialization and mild atherosclerosis of the dissecting aneurysm developed within twenty-three months.

The histologic structure of the parallel strands bridging the lumen of the new aortic channel indicates an origin from the frayed-out strands of elastic from the media, rather than intercostal arteries.

In approximately 10 per cent of the reported cases, dissecting aneurysm heals, is not the cause of death, and can be compatible with adequate functional capacity for years.

AUTHORS.

Gross, Harry, and Philips, Benjamin: Complete Occlusion of the Abdominal Aorta. Am. J. M. Sc. 200: 203, 1940.

Seven cases of complete occlusion of the aorta at its bifurcation, observed during the course of 5,350 autopsies, are presented.

Of these, four were patients with atherosclerosis of the coronary arteries and *aorta, two with diffuse vascular disease involving the venous system,* and one with chronic rheumatic cardiovalvular disease, auricular fibrillation, and a ball-valve thrombus of the left auricle.

Clinically, the classical picture usually associated with complete occlusion of the aorta at its bifurcation occurred in one case. In the remaining six, the clinical variations were probably due to: (1) differences in the rate of progression of the occlusion; (2) the presence of an adequate collateral circulation; and (3) subsequent development of a more efficient anastomotic circulation.

In two cases of peripheral arteriosclerosis, a rapid and progressive course with early bilateral involvement and the recurrence and progression of gangrene of the stump should have suggested the existence of an associated occlusive lesion of the aorta.

The difficulties inherent in making the differential diagnosis between thrombosis and embolism as the cause of complete occlusion are discussed.

AUTHORS.

Follis, Richard H., Jr.: The Coronary Arteries in Relation to Sudden Death During Anaesthesia. Bull. Johns Hopkins Hosp. 47: 211, 1940.

Three cases of sudden death during nitrous oxide, oxygen and ether anesthesia are presented. In two of them the right coronary orifice was very small, and the circumference of the right coronary artery was only one-half that of the left. In the third case there was extensive arteriosclerosis. These cases seem to re-emphasize the importance of the status of the coronary arterial system in relation to sudden death during anesthesia.

AUTHOR.

Gregg, Donald E., and Green, Harold D.: Registration and Interpretation of Normal Phasic Inflow Into a Left Coronary Artery by an Improved Differential Manometric Method. Am. J. Physiol. 130: 114, 1940.

A *method* is described for continuous optical registration of the instantaneous rate of inflow into *a* coronary artery. This involves shunting the blood from the

aorta to the coronary artery through a short external circuit containing an orifice (or other device) connected with a differential manometer.

The left coronary inflow curves so obtained demonstrate that beginning approximately at the onset of isometric contraction there is a rapid retardation of flow but that with the rise of aortic pressure during ejection the inflow rapidly accelerates, reaching a peak during the middle of the rise of aortic pressure and then declining to a more or less constant rate of inflow during the latter part of systole. Following the incisura there is again a rapid acceleration, the inflow reaching a peak early in diastole and then declining with the progressive fall of aortic pressure in diastole.

The inflow records are complicated by volume elastic effects due to the cyclic rise and fall of aortic pressure and by a compressor action of ventricular systole.

Despite these complications, and unless some other unknown factors are operating, it seems probable that the rate of inflow at the end of diastole, just preceding isometric contraction, can be used as an index of intramural flow during diastole.

Similarly it seems probable that the rate of inflow during the brief interval at, or just preceding, the onset of protodiastole, i.e., at the peak of the peripheral coronary pressure curve, can be used as an index of the systolic rate of intramural flow. In almost all instances the systolic intramural flow so measured is of sizable magnitude.

The rate of intramural flow per millimeter of differential pressure is greater during systole than during diastole.

Simultaneous measurement of aortic pressure and rate of intramural flow indicates that the resistance to blood flow existing during the latter part of diastole is increased from 2- to 4-fold during systole.

The total flow may be determined from the moment-to-moment flow curve by appropriate procedures.

AUTHORS.

Brightman, I. Jay, and Batterman, Robert C.: The Treatment of Edema by Rectal Administration of Diuretics. J. Lab. and Clin. Med. 25: 1038, 1940.

The mercurin and modified salyrgan suppositories produce only minimal changes in the rectal mucosa, but they may occasionally cause local discomfort and burning.

Mercurial diuretic suppositories may produce a definite and clinically effective diuresis, but their dependability is only 60 per cent.

The possible danger of administering a mercurial diuretic intravenously soon after a suppository is discussed.

AUTHORS.

Robertson, Harold F., and Faust, Frederick B.: Theophylline with Isopropanolamine in Heart Disease. With Especial Reference to Congestive Failure. J. Lab. and Clin. Med. 25: 1066, 1940.

The effect of theophylline with isopropanolamine was studied in a series of twenty-one patients, with reference to capillary dilatation, arterial, venous, and spinal fluid pressures. These pressures showed a definite fall associated with a capillary dilatation. This response to the drug, although comparatively brief, may prove useful in the treatment of congestive heart failure in conjunction with venesection and other appropriate measures. Further study may establish a more sustained effect with the oral or intramuscular administration of this preparation. Our observations showed considerable relief from dyspnea and orthopnea shortly

after injection, lasting from three to four hours. The clinical improvement was far more sustained than the laboratory studies indicate.

AUTHORS.

Kissane, R. W., and Koons, R. A.: Spontaneous Redigitalization Following Rapid Diuresis in Congestive Heart Failure. Tr. Am. Therap. Soc. 29: 111, 1940.

Forty-three cases of postdiuretic syndrome have been observed; some occurred accidentally and others were produced experimentally. The chief symptoms are marked bradycardia, nausea, vomiting, headache, weakness, extrasystoles, and coupled rhythm. Occasional transient auricular fibrillation or flutter will occur.

The primary factor in the production of this syndrome appears to be the reabsorption of digitalis substances from the edematous fluids; the secondary factor, the rate of elimination of this fluid through the kidneys with sufficient rapidity to prevent the elimination of these substances. It appears that both these factors must be present before the syndrome will occur. The syndrome does not appear to be due to mercurial diuretics since it occurred following rapid diuresis with glucose.

It is suggested that diuresis be produced slowly and digitalis be stopped until the amount of the reabsorption can be determined.

AUTHORS.

Starr, Isaac, and Ferguson, L. K.: B Methylcholine Urethane: Its Action in Various Normal and Abnormal Conditions, Especially Postoperative Urinary Retention. Am. J. M. Sc. 200: 372, 1940.

Beta methylcholine urethane, a stable choline derivative synthesized by Major at the suggestion of Simonart, has been studied in the clinic.

Having the typical choline action, this drug produces effects analogous to stimulation of parasympathetic nerves. These effects can be abolished by atropine. It is more stable than mecholyl and largely lacks the undesired nicotine-like action of doryl. It is probably for this reason that uncomfortable side effects are at a minimum. The authors regard it as superior to doryl for use in the clinic.

Given to twenty-five normal young adults, in suitable dosage, the drug caused increased peristalsis and a desire to void when its action on the heart and circulation, salivation, and sweating was minimal.

The drug caused emptying of the bladder in 68 per cent of 122 patients with postoperative urinary retention, reducing the necessity for catheterization by two-thirds.

It has also been used with benefit in patients with neurogenic bladders and in certain cases of abdominal distention, extreme constipation, and peripheral vascular disease.

AUTHORS.

Book Reviews

THE SOLDIER'S HEART AND THE EFFORT SYNDROME: By Sir Thomas Lewis. Second edition, 103 pages, Shaw and Sons, London, 1940. Price, 8/6.

The first edition of this book was prepared shortly before the close of the war of 1914-1918. The book has now been drastically revised—largely rewritten, in fact. It is not a treatise on heart disease, but a collection of information which is particularly applicable to the soldier.

As in the first edition, there are four major sections: the first deals with definition, etiology, symptoms, prognosis, and treatment of the effort syndrome; the second, with the diagnosis of heart disease in soldiers; the third, with the examination of recruits; and the fourth, which is less important, with medical reports of discharged soldiers. The quality of the book is up to Sir Thomas' high standard. Facts and statements are presented briefly, clearly, and forcefully, and are obviously backed up by a wealth of information and preparation.

The trend of the times indicates the need for this new, revised edition. Although the effort syndrome is encountered among civilians, it is much more important in military practice. The section on diagnosis of heart disease in soldiers is of particular value at present, in view of this country's national defense measures. The part which the members of the medical profession will be called on to play, especially those who will examine recruits, if compulsory military training is adopted, and those who will serve as cardiac consultants, requires that this subject be handled in an intelligent, coordinated way. This book is a condensed report and guide, and should be read by every cardiologist and consultant. All of the British experience is filtered out and condensed in its few pages.

HUGH MCCULLOCH.

ELECTROCARDIOGRAPHY: By Chauncey C. Maher, M.D., Assistant Professor of Medicine, Northwestern University, and Paul H. Wosika, M.D., Instructor in Medicine, Northwestern University. Ed. 3, 334 pages, 100 electrocardiograms, 42 diagrams, 5 roentgenograms, $4.00, Baltimore, 1940, The Williams and Wilkins Company.

The appearance of this work in its third edition speaks for its popularity and also for the need of a simple exposition of the important subject of electrocardiography. The authors have adopted a novel, clear, and concise method of explanation, both of its theory and practical application. The book is essentially a primer, and, as such, is excellent. There is a clear discussion of the anatomy of the conduction system. Diagrams are drawn with many of the electrocardiograms, pointing out topographically the anatomic and physiologic condition of the heart which is responsible for the abnormal mechanism. This is especially well done in the case of auricular flutter and fibrillation. This edition has been enlarged and its scope broadened, particularly with reference to correlation of the roentgenographic appearance of the heart with the electrical axis. Perhaps subsequent editions will consider such subjects as lateral wall infarction, pulmonary infarction, hypo- and hypercalcemia, acidosis, alkalosis, and acute nephritis.

This book is recommended to the beginner in electrocardiography; he will find it a convenient *stepping* stone to more extensive treatises. The type, paper, and binding are excellent, and aid in making the book attractive.

HAROLD FEIL.

CLINICAL HEART DISEASE; 2nd Edition: By Samuel A. Levine, M.D., Assistant Professor of Medicine, Harvard Medical School, Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston. W. B. Saunders Co., 1940, 477 pages, 109 illustrations.

The second edition of this deservedly popular book does not incorporate many important changes from the first edition, which appeared four years ago. However, the reader is informed that no great or fundamental advances in cardiology have taken place during that period.

The author, as is well known, has been an enthusiastic and tireless student of his subject for many years. He writes tersely and clearly and is willing to express his opinions on controversial subjects. Since those opinions are the result, not of desk research, but of careful, intelligent work and observation, they cannot fail to interest even those who have labored long in similar vineyards. The book is intended for general practitioners, and fulfills their everyday needs very well indeed. It should also be helpful to cardiologists, especially those who have not as yet been through the mill of arduous clinical training.

CHARLES C. WOLFERTH.

MANUAL OF PERIPHERAL VASCULAR DISORDERS: By David W. Kramer, M.D., Assistant Professor of Medicine, Jefferson Medical College. Philadelphia, 1940, 448 pages, 126 illustrations, $6.00, The Blakiston Company.

This book attempts to give the general practitioner and the specialist in peripheral vascular disease, *first*, a careful outline of the symptoms, signs, and tests, and, *second*, a classification of the various vascular disorders, their etiology, pathology, diagnosis, and treatment. The author has succeeded in the first part in presenting an orderly method of study and in describing accurately the various symptoms and signs. His description of diagnostic apparatus and tests is complete, and he gives a very fair estimation of their value. One hundred eighteen pages are given over to this important part of the book.

Part II would be better titled "The Occlusive Arterial Disorders," instead of "The Occlusive Vascular Disorders," for diseases of the veins are barely mentioned and the lymphatics are not included. No satisfactory classification of peripheral vascular diseases has thus far been presented. The author has made an earnest attempt to accomplish this, but leaves one a little confused. For instance, in Chapter 10 he includes diabetic arteritis under chronic forms, listing it with the so-called infectious group.

Chapters 16, 17, and 18, on vasospastic diseases, could be combined, for there is some reduplication, and all of the conditions which are described are very closely related.

One is glad to see a section on hypertension in a manual of this type.

The sections on treatment are well arranged, and the various types of therapy receive excellent evaluation. The author considers the economic factors in deciding what treatment to use, and attempts to avoid elaborate apparatus unless it is definitely indicated.

Part IV is entitled "Gangrene and Disorders of the Veins." One wonders why gangrene was not placed under arterial disease, for it is of relatively little importance in venous pathology. One is also disappointed in noting only 24 pages on

veins, and, moreover, no section or chapter on lymphatic disease. The bibliographies are satisfactory and plenty of case reports are included. Some of the illustrations, such as Figs. 2 and 22, fail to show at all, or clearly, what is intended. Other photographs are quite indistinct. The addition of more photographs, especially "before and after," with the case reports would be of value.

Finally, this book is essentially a manual for the practitioner. There is little that is new for the worker in this specialty. As compared to many recent books on peripheral vascular disease, it evaluates treatment in a much more unbiased way. It is almost entirely devoted to diseases which affect the arteries primarily, and, therefore, does not completely cover the field indicated by its title.

A. WILBUR DURYEE.

ACUTE MYOCARDITIS: By F. Wuhrmann. 148 pages, S. Karger, Basel.

This monograph may be of fundamental importance. Its purpose is to give a complete picture of a neglected condition, namely, acute interstitial myocarditis, originally described by Fiedler in 1897. The work is based on an original series of thirty-six cases. This is recorded in the beginning of the book. Fifteen of the cases occurred in patients with pulmonary tuberculosis. The second half is given over to a general description. The condition is well circumscribed and may be distinguished from the changes which follow diphtheria, scarlet fever, sepsis, and rheumatism.

A review of the not very numerous cases in the literature and eighty-six illustrations, which are very clear, follow. Altogether, this is a most commendable work.

JULIUS JENSEN.

PHONOCARDIOGRAPHIC AND HEMODYNAMIC STUDIES IN PREGNANT WOMEN AND FETI DURING THE LAST MONTHS OF NORMAL PREGNANCY: By Julio C. Pereira. 114 pages, Buenos Aires, 1939.

By the direct method of Wiggers and Dean, the author recorded the phonocardiograms of forty-nine normal women and found no essential difference between these and records obtained from men. Nor did fifty pregnant women show any important difference.

The author also recorded the fetal phonocardiogram, and found that the first sound has a duration of 0.105±0.0024 second, and is composed of 3.8±0.088 vibrations, with an average tracing amplitude of 9.41±0.348 mm. The second sound has a duration of 0.07±0.0015 second, is composed of 2.59±0.0539 vibrations, and has a vibration amplitude of 6.28±0.1723 mm.

The author believes that these results are more accurate than the discrepant ones obtained with the Cambridge stethograph.

The average fetal heart rate was 141. The duration of systole decreases as the rate increases.

Altogether, this constitutes an elaborate and careful statistical study, richly illustrated.

JULIUS JENSEN.

STUDIES ON VENOUS PRESSURE DURING VALSALVA'S EXPERIMENT: By Knut Liedholm. Acta med. Scandinav., 213 pages, Suppl. 106 (Lund), 1939.

This is a most detailed and elaborate analysis of Valsalva's experiment, with special study of the venous pressure. The author justifies his effort by stating that Valsalva's experiment is by no means exclusively a laboratory test, but a mechanism which functions with every sudden muscular effort. In view of the attention which recently has been paid to venous pressures in general, this behavior during Valsalva's experiment may be important. The author then analyzes the nature of Valsalva's

experiment and the literature on its effect on the circulation: the size of the heart, stroke and minute volume, arterial pressure and venous pressure, heart rate, and changes in the capillaries.

The author then describes his elaborate technique for the simultaneous kymographic registration of thoracic and abdominal breathing and venous and arterial pressure. The methods for measurement of these phenomena are then elaborately discussed.

The author has subjected twenty-nine persons with normal cardiovascular systems, twenty-eight with hypertension, and forty-five with valvular lesions of the heart to his experiments. In the analysis of his observations, relatively slight emphasis has been placed on the state of compensation of the patient.

There is an elaborate analysis of the effect of respiration on the venous pressure; in some persons the venous pressure sinks during inspiration, and in others it rises. The reason for this discrepancy is not clear.

The increase in intrathoracic pressure during Valsalva's experiment is often followed, in a few seconds, by an increase in venous pressure which continues gradually until a certain maximum is reached. In extreme cases this may reach 71 cm. of H_2O. The curve proceeds at the same rate of incline till the top is reached. When the intrathoracic pressure is released, the venous pressure again falls at an even rate until it approaches the normal level, when it gradually flattens out. This function is then submitted to a most complete and elaborate mathematical analysis. Taken as groups, the normal persons showed the highest increase in venous pressure, those with valvular lesions the second highest, and those with hypertension the poorest response. This difference Liedholm ascribes to lowered vital capacity, i.e., impaired compensation; yet he does not enter further into the relation. He does not consider Valsalva's experiment suitable for a test of cardiovascular function. The decrease in venous pressure is largely influenced by respiration. A great many curves and statistical tables are included in the work. There are finally, a summary in English and ten pages of references.

With the exception of the relation of Valsalva's experiment to decompensation (which I should consider of some importance), this work leaves little to be said about Valsalva's experiment. The references appear to cover all essential literature on the venous pressure.

JULIUS JENSEN.

LA CIRCULATION DE RETOUR: By André Jouve and Jean Vague, 180 pages, no illustrations, 1940, Masson et Cie., Paris.

The title of this monograph cannot be translated directly into English without creating a misconception, for "venous return" is used in a different sense in America. The book is concerned with the anatomy, physiology, and pathology of that part of the circulation, including the blood depots, which lies between the venules and the tricuspid valves. The veins form the principal part of the system; they are conceived of as reacting as a unit to physiologic and pharmacologic agents, as having control of the amount of blood in the depots, and as being a chief factor in the distribution of blood between the various parts of the circulation. The relationship of this system to the commoner conditions of disease is the main subject of this book.

The authors' most interesting contribution to the subject has been secured by means of a new clinical test to demonstrate the presence or absence of an excess of blood in the "circulation de retour." With the subject in the horizontal position, the pressure is recorded with a manometer which is connected to a needle in a vein near the elbow. The legs are then passively elevated at an angle of 60° for fifteen seconds, and then lowered to the horizontal for fifteen seconds; following this, the right upper quadrant of the abdomen is compressed with both hands for fifteen

seconds. The venous pressure is measured at fifteen-second intervals. In normal subjects, these maneuvers do not affect the venous pressure; if they elevate it, the test is positive.

From their own observations, and from estimations of venous pressure, blood volume, blood velocity, and cardiac output which they have gathered largely from the literature, together with the clinical manifestations, the authors attempt to draw a picture of what is happening in the circulation in each of the commoner diseases, with emphasis on the role of the veins and depot organs. The examples which follow are chosen from those which are most novel to Americans.

Congestion in heart failure is believed to be a manifestation of increased blood volume. It is of two types, namely, hypervolemia with high venous pressure, and hypervolemia with relatively low venous pressure. The difference between them is attributed to the degree of venous constriction, which may be a compensatory reaction to support a weakened heart, but also, under certain conditions, may cause further cardiac embarrassment.

In addition to arterial hypertension caused by arteriolar constriction, the authors speculate about another form which is primarily the result of venous constriction; by increasing cardiac filling, this would increase cardiac output, thus raising blood pressure against normal arteriolar resistance.

Lack of tone of the venous walls, in addition to many other factors, is believed to play a large part in shock and collapse.

These and the other theories which are discussed are put forward modestly as working hypotheses only. The multiplicity of factors involved and the difficulty of evaluating them are repeatedly emphasized by the authors.

It is not hard to criticize the book. The chapter on treatment is the most unsatisfactory part. The American school is far more critical of therapeutics than the French, and, in the absence of any evidence whatsoever, will hesitate to admit the value of a large number of drugs, baths, and other agents which, in addition to standard remedies, are said to benefit patients, sometimes by acting on the veins. One wishes that more factual data had been given, and that the relation between the facts and some of the theories had been set forth more clearly. Although many authors are mentioned by name, the reader who is concerned with the facts is handicapped by a complete lack of specific references. There is no bibliography in the book.

This monograph makes a serious attempt to improve our conceptions of diseases of the circulation. The old theories which endeavored to explain all the phenomena of circulatory disease in terms of heart and arterioles are certainly outmoded, so that this presentation is timely and stimulating. It is difficult to say how successful the authors have been, for they are working in a field in which it is hard to secure convincing evidence, either for or against their views, but the same criticism could be made about many current theories concerning the heart and circulation which students of the subject are sometimes inclined to accept, more because they are familiar than because they can be supported by convincing evidence. Therefore, this monograph should be read by all who are interested in cardiovascular theories; it will stimulate some hard, and much needed, thinking.

All Americans will join in the hope that the vicissitudes of war have not interrupted the authors' work.

ISAAC STARR.

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generation experiments upon the vagi are quite conclusive. Anrep[4] found the same vagus influence in his experiments with both the denervated and the innervated heart-lung preparation. Rein[5] and Hochrein and Keller[6] have employed the thermostromuhr method of the former to arrive at the same conclusion. (2) Stimulation of the stomach, as by distention, initiates afferent impulses in the vagus nerve. These are followed by efferent vagus impulses of central reflex origin. It is the latter which, in our opinion, lead to coronary vasoconstriction. This type of reaction may be considered one of the vagovagal reflexes.

EXPERIMENTAL PROCEDURE

Fifteen large, healthy dogs, which were anesthetized with dial (Ciba), or, preferably, with Gréhant's mixture, were used. A carefully calibrated thermostromuhr of the "direct current heater" type[7] was applied to the circumflex branch of the left coronary artery. The dog's chest was then closed. Continuous photographic records of the coronary blood flow and the blood pressure and pulse from a femoral artery were made. When these became stabilized, a dose of a drug known to be a coronary dilator (theobromine sodium acetate, 60 mg., aminophyllin, 50 mg., or adenylic acid, 3 mg.) was given intravenously. If the response to this medication was satisfactory, it was known that the circulatory system was capable of reacting, and that the thermostromuhr was well placed and was functioning. A large balloon was then placed in the stomach and was inflated with varying amounts of air. The best results were obtained when about 600 c.c. of air were introduced and when the intragastric pressure was raised to 10 or 15 mm. of mercury. On a few occasions a higher pressure (40 to 60 mm. of mercury) was employed, but this was less satisfactory, apparently because it produced a sudden, large increase of venous pressure. In most of the animals, several observations on the effect of stomach distention were made before and after the administration of atropine or the performance of vagotomy. In some of the animals, also, air was introduced into the

TABLE I

SUMMARY OF EXPERIMENTAL DATA

EXPERIMENT NO.	ANESTHETIC	BEFORE ATROPINE. INFLATION OF:		AFTER ATROPINE. INFLATION OF:		VAGUS SECTION			
						BEFORE		AFTER	
		STOMACH*	PERITONEUM	STOMACH	PERITONEUM	STOMACH	PERITONEUM	STOMACH	PERITONEUM
1	Dial		+						
2	Dial		−						++
3	Dial								
4	Dial	−o	+						
5	Dial	−	+						
6	Dial	o+		o					
7	Dial	−+		o	+				
8	Dial	−							
9	Dial	−−+							
10	Gréhant	+−		−+					
11	Gréhant	−−							
12	Gréhant	−	−		+				
13	Gréhant	−	−	o	o				
14	Gréhant					−−		oo	
15	Gréhant					−−		o+	

*o, coronary flow unchanged after inflation of stomach or peritoneal cavity
+, coronary flow increased after inflation of stomach or peritoneal cavity
−, coronary flow decreased after inflation of stomach or peritoneal cavity

peritoneal cavity through a trocar until the abdomen was visibly distended. This was also repeated after the vagi had been sectioned or after atropine (0.0013 Gm.) had been given. Tables I and II summarize our experimental data.

TABLE II

SUMMARY OF THE DATA OF TABLE I

EXPERIMENTAL CONDITIONS	CORONARY ARTERY BLOOD FLOW:			
	UNCHANGED	INCREASED	DECREASED	TOTAL
Stomach distention before atropine or vagotomy	2	4	15	21
Stomach distention after atropine or vagotomy	5	5	1	11
Peritoneal distention before atropine or vagotomy	0	3	3	6
Peritoneal distention after atropine or vagotomy	1	4	0	5

RESULTS

The dogs' stomachs were distended twenty-one times before drugs were given or the vagi sectioned. In fifteen instances the coronary blood flow decreased. The decrease was definite, ranging from 15 per cent to 35 per cent, and was usually accompanied by little or no change in the blood pressure and pulse rate. Fig. 1 is a portion of a typical tracing from such an experiment. Marked distention of the stomach, as a matter of fact, quite frequently increased the pulse rate and the systolic blood pressure; under these circumstances, the occurrence of a

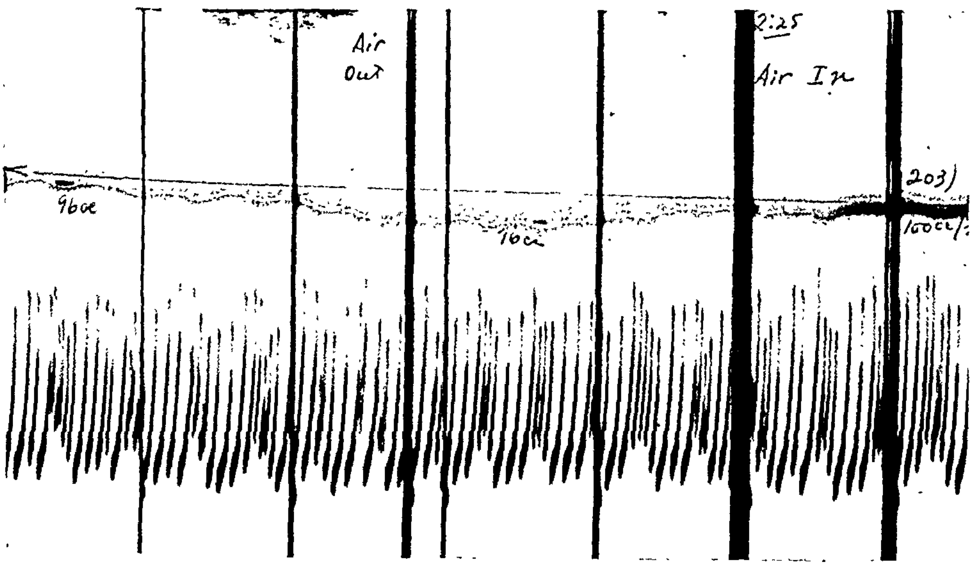

Fig. 1.—April 17, 1939, Gréhant anesthesia was used. Tracing runs from right to left. Fig. 2.

decrease in coronary flow was especially significant. Fig. 2 was drawn from the photographic curves of a typical, complete experiment. Moderate inflation of the stomach caused the pulse rate to increase while the coronary flow remained practically unchanged. Further distention

(to 25 to 30 mm. of mercury) resulted in a distinct diminution of coronary flow, together with a distinct increase of the systolic blood pressure and the pulse rate.

After the administration of atropine, or the cutting of both vagi, the dogs' stomachs were inflated eleven times. The coronary flow decreased once, increased five times, and remained unchanged five times (Fig. 2).

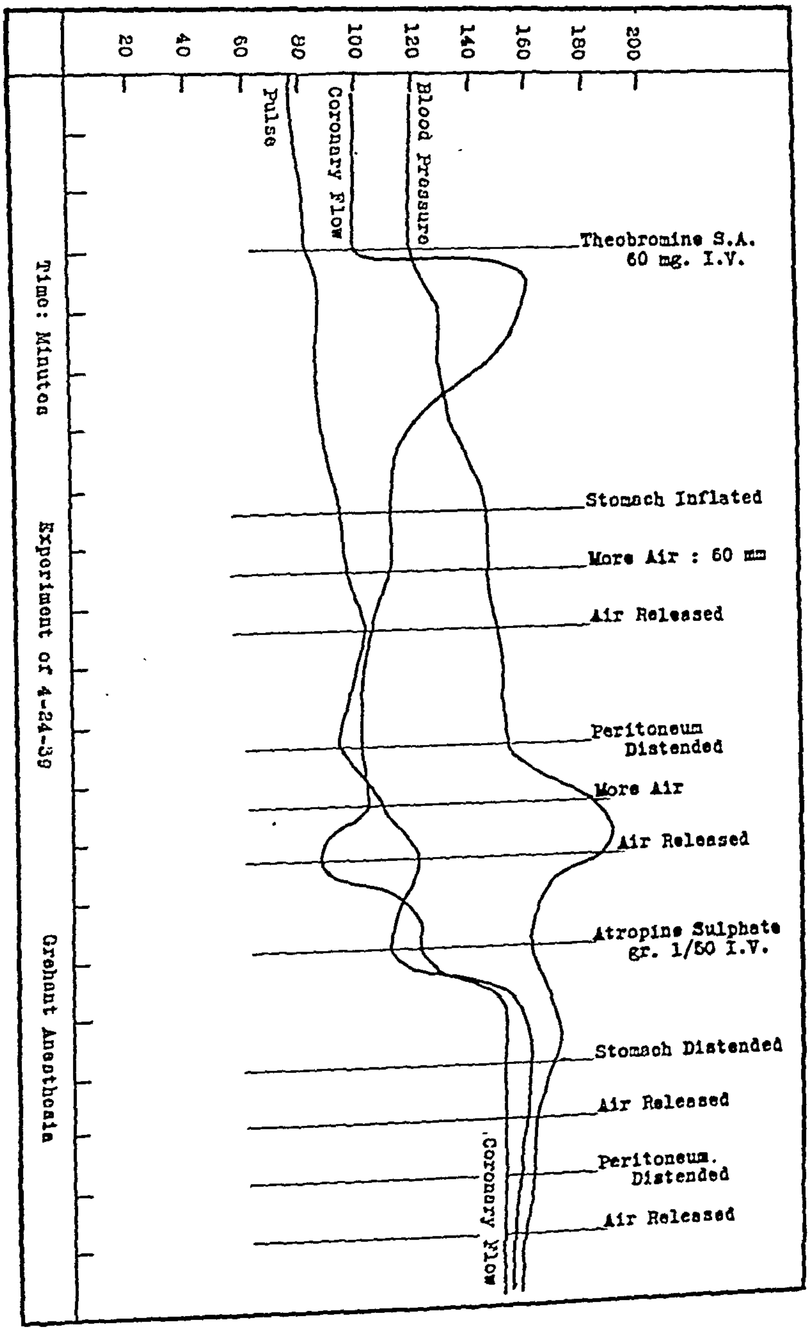

Fig. 2.

It was found that when the balloon was placed in the fundus, or partially in the cardia, the deterrent effect on the coronary flow was greater than when it was placed more centrally in the stomach. Tugging on the inflated balloon seemed to have little additional effect. This observa-

tion seems to favor our interpretation, namely, that the reduction in coronary flow is caused by reflex nervous action, rather than by mechanical displacement. Further light was cast on this point by the results which we obtained when the peritoneal cavity was distended. This was done six times before the vagi were interfered with; the coronary flow increased three times and decreased three times. The effect of this type of inflation is illustrated in Fig. 2; the blood pressure increased while the coronary flow decreased. After the administration of atropine in this experiment, the coronary flow remained unchanged when the peritoneal cavity was again inflated. After atropine administration or bilateral vagotomy, the peritoneal cavity was distended five times. The coronary flow increased in four instances and was unchanged in one.

DISCUSSION

In the absence of reflex coronary vasoconstriction, one might naturally expect that a sudden rise in the intra-abdominal pressure would increase the venous return flow to the heart. In accordance with Starling's law, and as a result of reflexes like the Bainbridge reflex, the blood pressure, pulse rate, and cardiac output should increase temporarily. Ordinarily, any or all of these three factors would augment the coronary blood flow. The fact that in many of our experiments the coronary flow decreased when augmentation should have occurred argues for a reflex coronary vasoconstriction. The abolition of this unfavorable reaction by the administration of atropine or by bilateral vagotomy would seem to implicate the vagus nerve as the mediator of the reflex. The existence, or the operation, of such a reflex is obviously disadvantageous to the heart. Previous attempts to elicit this reflex experimentally, not only in our laboratory but elsewhere, were not successful, except in the case of von Bergmann,[8] whose results parallel ours. It seems probable that unsuitable, or too deep, anesthesia or excessive distention of the viscera may have been responsible for the negative results in the past. In our present study, many experiments were quite unsatisfactory because of these factors. Furthermore, since this reflex may be only one of many influences converging, at a given time, on the coronary arteries, it is quite probable that it may frequently fail to exert an effect, or may be overwhelmed by other factors.

Finally, it is fair to conclude that if such a reflex operated at a time when the margin of reserve between the myocardium's need for blood and the coronary circulation's ability to supply it was small, an attack of angina pectoris might be precipitated.

CONCLUSIONS

1. In carefully performed experiments on dogs, using light anesthesia, distention of the stomach or peritoneal cavity initiated, in many instances (but not always, because of differences in the reactions of individual animals), a vagovagal reflex which caused a decrease in the

flow of blood through the circumflex branch of the left coronary artery.

2. The mechanism of some of the attacks of angina pectoris in patients with distended stomachs is made clear by this study.

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THE EFFECT OF TRANSPLANTED ISCHEMIC KIDNEYS AND OF TEMPORARY, COMPLETE, RENAL ISCHEMIA UPON THE BLOOD PRESSURE OF RABBITS

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HOUSSAY, Taquini, and their co-workers[1] have made certain observations which are of fundamental importance in the study of experimental hypertension. They were able to demonstrate that transplantation of the ischemic kidneys of dogs with Goldblatt hypertension[2] caused an almost immediate rise in the blood pressure of the recipient animal after anastomosis of the renal and carotid-jugular vessels. A more pronounced rise took place if the animals into which the transplantation was made had been previously nephrectomized. An attempt to confirm these results on another animal appeared to be of sufficient importance to justify the experiments reported in this paper.

The rabbit was chosen because, like the dog, it lends itself to the production of hypertension by means of artificial renal ischemia.[3] The hypertension in this animal appears to be identical with that in the dog; furthermore, it can be extremely severe, to the extent of attaining the so-called malignant phase, with widespread, necrotizing arteriolitis.[4]

Transplantation of Ischemic Kidneys of Hypertensive Rabbits Into the Necks of Rabbits With Normal Blood Pressure

METHOD

Hypertension was produced in rabbits by means of renal ischemia.[2, 5] Rabbits which were approximately three weeks old, and weighed between two and three hundred grams, were anesthetized with ether, and the left renal pedicle was exposed through an abdominal incision. A wire, 0.55 mm. in diameter, was placed alongside the renal artery, and a silk ligature tied snugly about both vessel and wire, after which the wire was withdrawn. When the rabbit weighed approximately 1500 grams, the healthy kidney was removed. Following the nephrectomy, a pronounced rise in blood pressure developed in most instances within the course of a few weeks, often reaching extremely high levels. These animals died as a result of widespread hemorrhage caused by vascular lesions. Only animals with a definite and persistent hypertension were used in the transplantation experiments. By palpation of the kidneys through the abdominal wall, a difference in their size could be detected with reasonable accuracy. It was found that if the ischemic kidney was too small, i.e., less than approximately 2.5 centimeters in length, removal of the normal kidney usually led to rapidly fatal uremia. On the other hand, if the length of the ischemic kidney exceeded three centimeters, unless the normal kidney was longer by about six millimeters, its removal resulted in only a small rise of blood pressure, or none at all.

Two methods were used in estimating the blood pressure. The systolic pressure in the central artery of the ear was measured by means of Grant and Rothschild's

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capsule.[6] Provided certain precautions are observed, this method has proved to be very reliable.[3] The blood pressure was also measured by the Riva-Rocci method in the following way: the rabbit was tied to an animal board, a blood pressure cuff wrapped around the abdomen, and a diaphragm stethoscope placed under the cuff over the abdominal aorta. Both systolic and diastolic pressures could usually be measured by auscultation.

TECHNIQUE OF TRANSPLANTATION

It was found necessary to modify the technique described by Houssay,[1] because of the small size of the renal vessels of the rabbit. The following method was devised after many unsuccessful trials. The normal animal was anesthetized, and its head immobilized in the clamps of a specially devised frame. The latter was provided with movable arms which held the cannulas, and with an adjustable receptacle for the ischemic, "hypertensive" kidney. The anastomoses were performed in the following manner: the carotid and jugular vessels were tied and severed, and the corresponding cannulas were placed over their proximal ends, which, in turn, were slipped into position over the ends of the specially designed arms. The projecting portions of the vessels were then everted over the cannulas and securely tied; meanwhile, the vessels themselves were occluded more proximally by rubber bands. A few drops of dilute heparin solution were placed in the open lumina of the vessels to prevent coagulation. The solitary, ischemic kidney of the hypertensive animal was then removed, and the renal vessels were slipped over the corresponding carotid and jugular vessels and held firmly in place by snapping the "rings" over the cannulas. Thus an intima-to-intima anastomosis was established. The adjustable arms were then removed, to prevent undue tension on, or torsion of, the vessels, and the rubber bands released to re-establish the circulation of the transplanted kidney. The details of the technique may be seen in the accompanying diagrams (Fig. 1). The blood pressure in the femoral artery was recorded on a moving drum.

Systemic anticoagulants were not necessary, for there was an interval of only about five minutes between removal of the kidney and restoration of its circulation. If the interval was longer, clots frequently formed within the renal vessels, rendering the transplant unsuccessful. Nembutal was employed as the anesthetic agent for both donor and recipient. This drug has been found to have only a slight effect on blood pressure, and less inhibiting effect on the pressor action of the renal pressor substance than other anesthetics, as, for instance, urethane.[7] In several instances, 1 per cent chloralose in 2 per cent gum acacia solution was used because it was the anesthetic recommended by Fasciolo, et al.,[1f] but it was found to be more toxic than nembutal.

That the blood supply to the transplanted kidney was adequate was clearly indicated by the following observations. Urinary secretion was resumed in some instances as early as two or three minutes after the transplantation had been completed. One experiment was continued for eleven hours, and active secretion of urine continued during the entire period. When the carotid artery was temporarily occluded, the transplanted kidney immediately shrank in size and became soft and pale; upon release of the arterial clamp the kidney speedily regained its original size and color. When the renal or jugular vein was temporarily occluded, the kidney became engorged within two or three seconds, and became cyanotic and increased in size and firmness; upon release of the venous clamp the kidney rapidly assumed its former appearance and consistency. The injection of a small amount of epinephrine into the transplanted kidney was followed by a prompt and appreciable rise of blood pressure. When a small cut or puncture wound was made in the cortex of the transplanted kidney, arterial blood oozed from it immediately.

The following successful transplantations were made: *Group 1.*—Kidneys of hypertensive rabbits were transplanted into eleven animals that

had normal blood pressures. In five, bilateral nephrectomy had been performed twenty-four to forty-eight hours previously; in the remaining six, the kidneys had not been removed. *Group 2.*—In two instances, normal kidneys were removed and kept at temperatures of 22° and 37° C., respectively, for a period of two hours before transplantation.

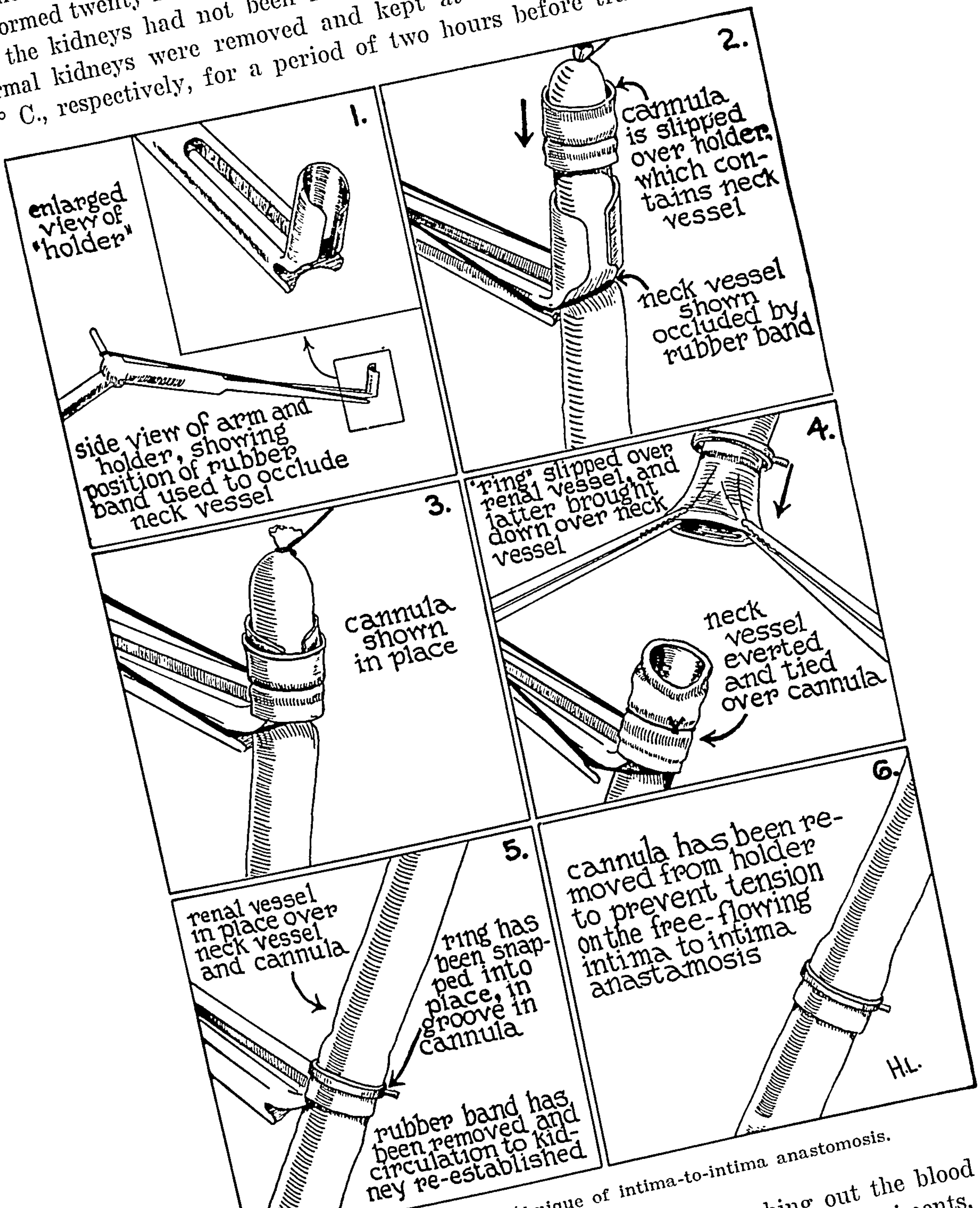

Fig. 1.—Details of technique of intima-to-intima anastomosis.

In these kidneys, clotting was prevented by washing out the blood immediately with Ringer's solution. *Group 3.*—In five experiments, kidneys of nonhypertensive rabbits were transplanted into normal animals.

RESULTS

In ten of the eleven experiments *(Group 1)*, transplantation of the "hypertensive," ischemic kidneys produced an immediate, but transient, fall in blood pressure of 10 to 20 mm. of mercury. The pressure gradually returned to its previous level in almost all instances (Fig. 2, Table I), but did not exceed the control level in a single animal (measurements were made over periods of ten minutes to eleven hours following reestablishment of the circulation). In the eleventh animal the blood pressure rose about 10 mm. Hg, and maintained the higher level for about fifty minutes. In this experiment the kidneys had not previously been removed (Table I).

TABLE I

EFFECT ON BLOOD PRESSURE OF TRANSPLANTED ISCHEMIC KIDNEYS FROM HYPERTENSIVE RABBITS

ANIMAL	B.P. BEFORE HYPERTENSION	B.P. AT TIME OF TRANSPLANTATION	DURATION OF HYPERTENSION	EVIDENCE OF MALIGNANT HYPERTENSION	ALTERATION OF RECIPIENT'S B.P. AFTER TRANSPLANTATION	VENTRICLE WT. / BODY WT. × 10^3	
Normal recipients							
RA 74	120/85	180/140	76 days	0	Transient fall of 5-10 mm.	9.3 / 3,150	2.96
RA 85	–	194/160	72 days	0	Transient fall of 5-10 mm.	9.1 / 3,250	2.80
RA 51	–	210/160	169 days	0	Transient fall of 5-10 mm.	10 / 2,680	3.74
RA 107	–	240/200	43 days	+	10 mm. rise in 30 secs.	6.6 / 2,080	3.18
RA 118	140/90	230/190	16 days	+	Transient fall of 5-10 mm.	5.8 / 2,350	2.50
Nephrectomized recipients							
RA 102	130/100	220/170	65 days	+	Transient fall of 5-10 mm.	9.8 / 3,155	3.12
RA 117	130/85	204/160	12 days	+	Transient fall of 5-10 mm.	6.2 / 2,060	3.00
RA_2 28	135/100	174/114	36 days	0	Transient fall of 5-10 mm.	7.4 / 2,975	2.44
RA_2 17	–	220/150	11 days	+	Transient fall of 5-10 mm.	6.8 / 2,090	3.25
R 13	–	220/190		+	Transient fall of 5-10 mm.		
Average							3.01*

*Average for ten normal rabbits selected at random was 2.43.

Completely negative results were also obtained in the two instances in which totally ischemic kidneys were transplanted *(Group 2)*, and in the five in which normal kidneys were transplanted *(Group 3)*.

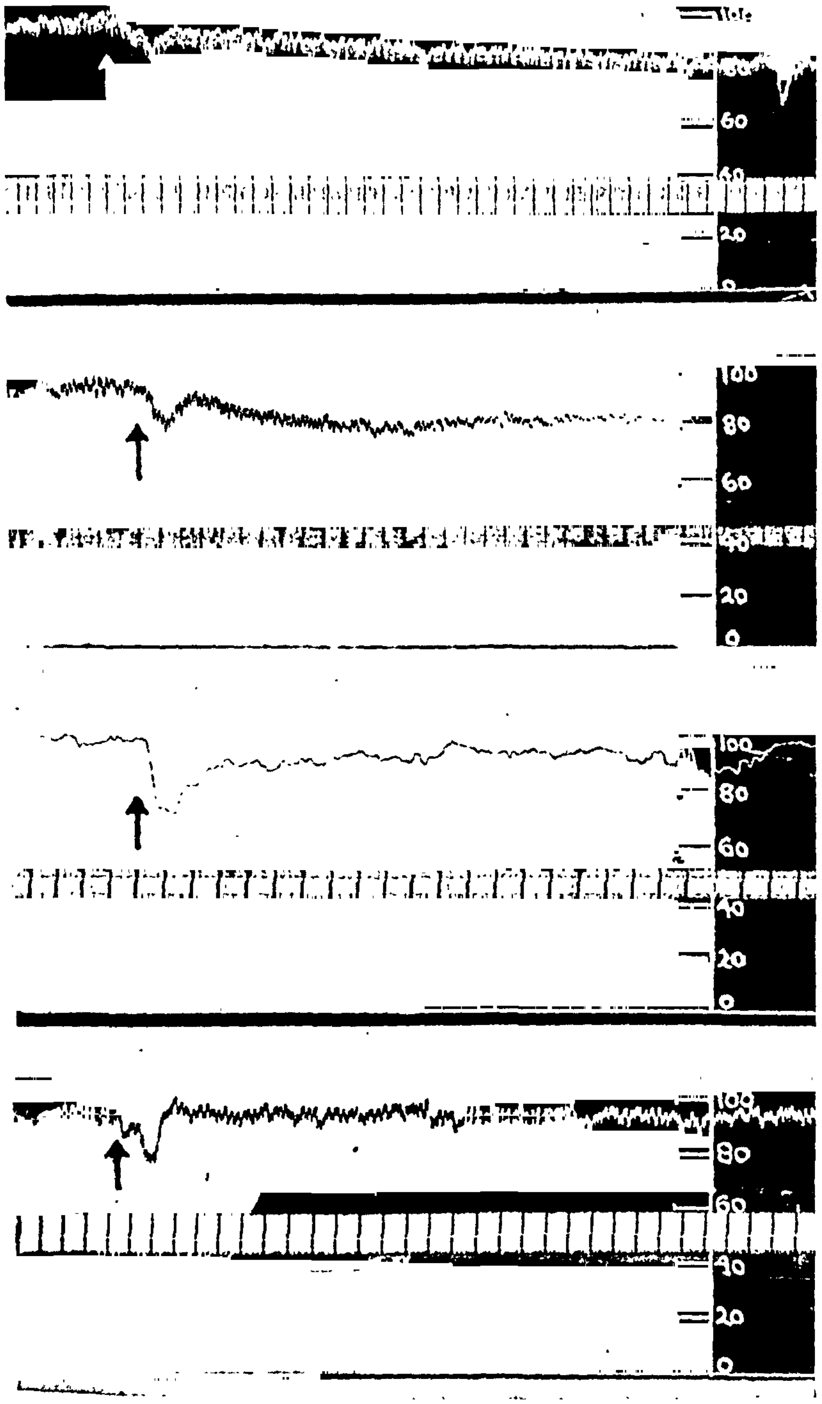

Fig. 2.—Effect of transplanted ischemic kidney on recipient's blood pressure. Circulation of kidney re-established at point of arrow. No rise in blood pressure. Time marker, 15-second intervals.

DISCUSSION

It may be seen that in only one of eleven rabbits was transplantation of the ischemic kidney followed by a rise in blood pressure, and that the elevation in this solitary instance was of small magnitude and short

duration. In view of the negative results in the other ten experiments, it is possible that this rise represented a spontaneous variation of the blood pressure, unrelated to the transplantation.

Considering the consistent and definite elevation reported by Houssay and his coworkers,[1] it is difficult to explain the failure of the blood pressure to rise in these experiments. For the following reasons, the objection cannot be made that our rabbits did not show a sufficient degree of hypertension.

1. Only rabbits which exhibited a significant and persistent elevation of blood pressure were employed, and the readings were checked by two different methods, as described above.

2. In six of the eleven animals the malignant phase of hypertension had been reached, for necrotizing arteriolitis was found in the post-mortem histologic sections. These animals were sacrificed only a short time before they were expected to die as a result of their hypertension.

3. In all instances the heart weights indicated definite cardiac hypertrophy (Table I).

Moreover, it cannot be argued that the transplanted kidneys did not receive an adequate blood supply; evidence concerning this point has already been presented.

The Effect Upon the Blood Pressure of Re-establishing the Circulation of Completely Ischemic Kidneys

In view of the negative results of the first series of experiments, an effort was made to confirm in rabbits the following observation of Taquini and his co-workers.[8] After clamping the renal pedicles of dogs for six or seven hours, and re-establishing the circulation by removing the clamps, they noted an immediate and conspicuous rise of blood pressure, an observation which we have confirmed on dogs and cats.[9]

METHODS AND RESULTS

Three series of experiments were carried out. In the first series, seven rabbits were anesthetized with nembutal, the abdomen was opened, and the right kidney removed. The left kidney was then freed from all attachments except the pedicle, and a bulldog clamp was placed across the renal artery, renal vein, and ureter. The abdomen was then closed, and the animal allowed to recover from the anesthetic. Three to five hours later the animal was again anesthetized with nembutal, the carotid was cannulated, and the blood pressure was recorded continuously. The abdomen was then reopened and the clamp released. In no instance was there a rise in blood pressure above the control level (Fig. 3, Table II).

In these experiments it was important to satisfy two requirements: (1) there should be no circulation in the kidneys while the clamps were

in place, and (2) an adequate circulation should be re-established upon removal of the clamps. Whether or not the first requirement was fulfilled was ascertained by puncturing the cortex after the pedicle had been clamped; failure to bleed or slight venous oozing was taken to indicate cessation of the renal circulation.

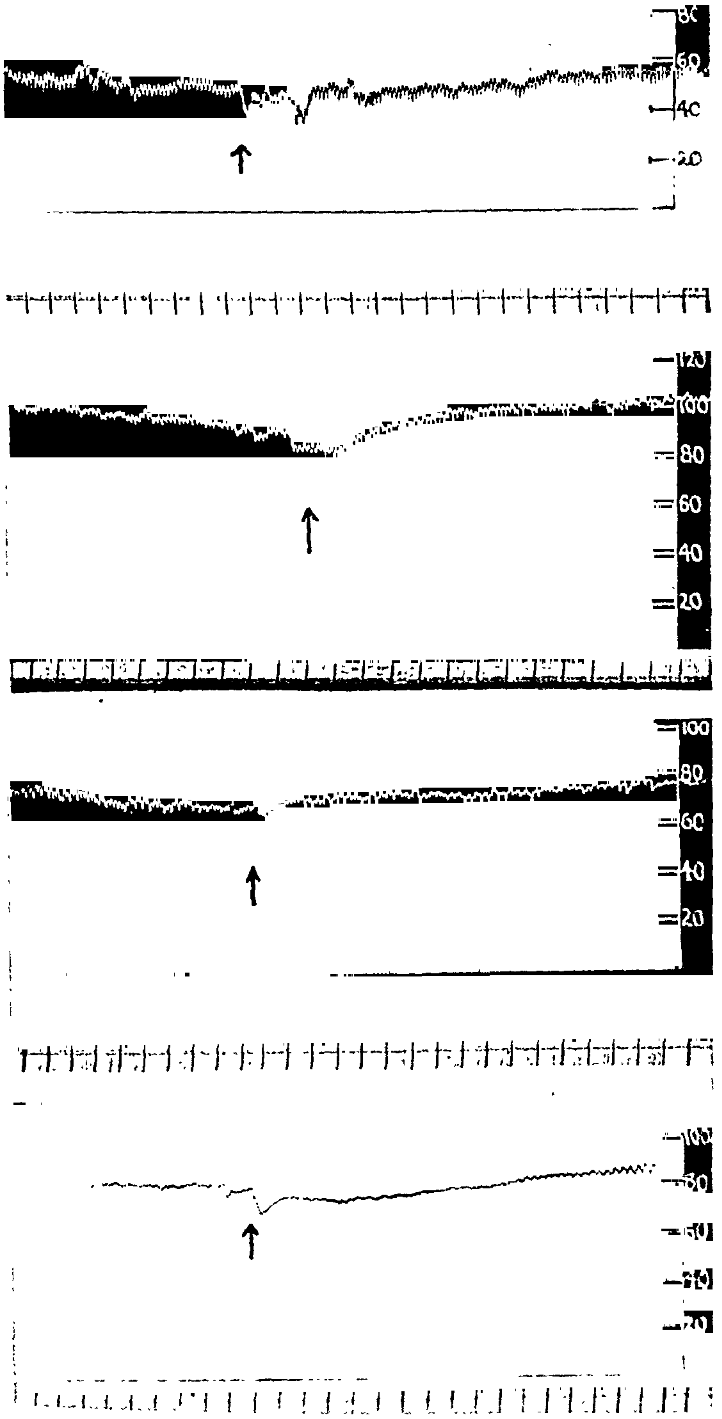

Fig. 3.—Effect on blood pressure of clamping left renal pedicle. Right kidney previously removed. Clamp removed at point of arrow. No rise of blood pressure. Nembutal anesthesia. Time marker, 15-second intervals.

TABLE II

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS. PEDICLE LEFT KIDNEY CLAMPED; RIGHT KIDNEY REMOVED. NEMBUTAL ANESTHESIA

ANIMAL	TIME CLAMPED	RISE OF B. P.	FALL OF B. P.	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEY	RECLAMPED	RISE OF B. P. ON SECOND INJECTION OF EPINEPHRINE INTO KIDNEY	RISE OF B. P. ON INTRAVENOUS INJECTION OF EPINEPHRINE
C 1	5 hr.	0	0	+			+
C 2	5 hr.	0	0	+			+
C 3	5 hr.	0	0	+			+
C 4	5 hr.	0	0	+			+
C 5	3 hr.	0	0		+	+	+
C 6	4 hr.	0	0		+	+	+
C 7	6 hr.	0	0		+	+	+

In three experiments, after it had been noted that removal of the clamp was not followed by an elevation of the blood pressure, the pedicle was again clamped. After three hours, 0.2 mg. of epinephrine was injected into the ischemic kidney. During the next few minutes no rise in blood pressure occurred; the clamp was then removed for the second time, and immediately there was an epinephrine pressor reaction (Fig. 4, Table II). When a like amount of epinephrine was injected intravenously after the blood pressure returned to normal, the resulting pressor effect was usually similar to that which followed the previous injection into the kidney. Failure of the blood pressure to rise after the injection of epinephrine into the kidney while the clamp was in place indicated that, if there was any renal circulation at the time, it was too minute to wash out a detectable amount of epinephrine into the general circulation. By the same token, the rise in pressure following release of the clamp demonstrated that the renal circulation had been restored. These experiments indicated that if a sufficient amount of pressor substance of the nature of epinephrine had accumulated in the kidney during the period of ischemia, a systemic pressor reaction would have occurred upon re-establishment of the renal circulation.

It has been demonstrated that anesthesia of any type interferes with the pressor effects of renin.[7] In order to exclude the possibility that anesthesia interfered with pressor responses in the above experiments, a second series of ten experiments was performed upon unanesthetized rabbits in the following manner. Under ether anesthesia, the abdomen was opened, the right kidney removed, and the left kidney freed from all attachments except the pedicle. A rubber band lubricated with vaseline was looped around the pedicle, and the ends of the rubber band were left extruding through a stab wound in the loin. To the center of this elastic loop was tied a ligature which, in turn, led through the abdominal wall. The rubber band was then pulled taut enough to

occlude the vessels of the pedicle, and tied externally with a silk ligature. That the constriction of the pedicle was effective was shown by the fact that there was no bleeding, or only slight venous oozing, when the cortex was punctured. In three of the six experiments in which this technique was followed the ligature was placed only about the renal artery. The animals were then allowed to recover from the anesthetic. Three to seven hours later, the blood pressure in the rabbit's ear was estimated by means of Grant and Rothschild's capsule, according to the method previously mentioned.[3] After a constant baseline had been established, the ends of the rubber band were cut, and the loop was pulled from the

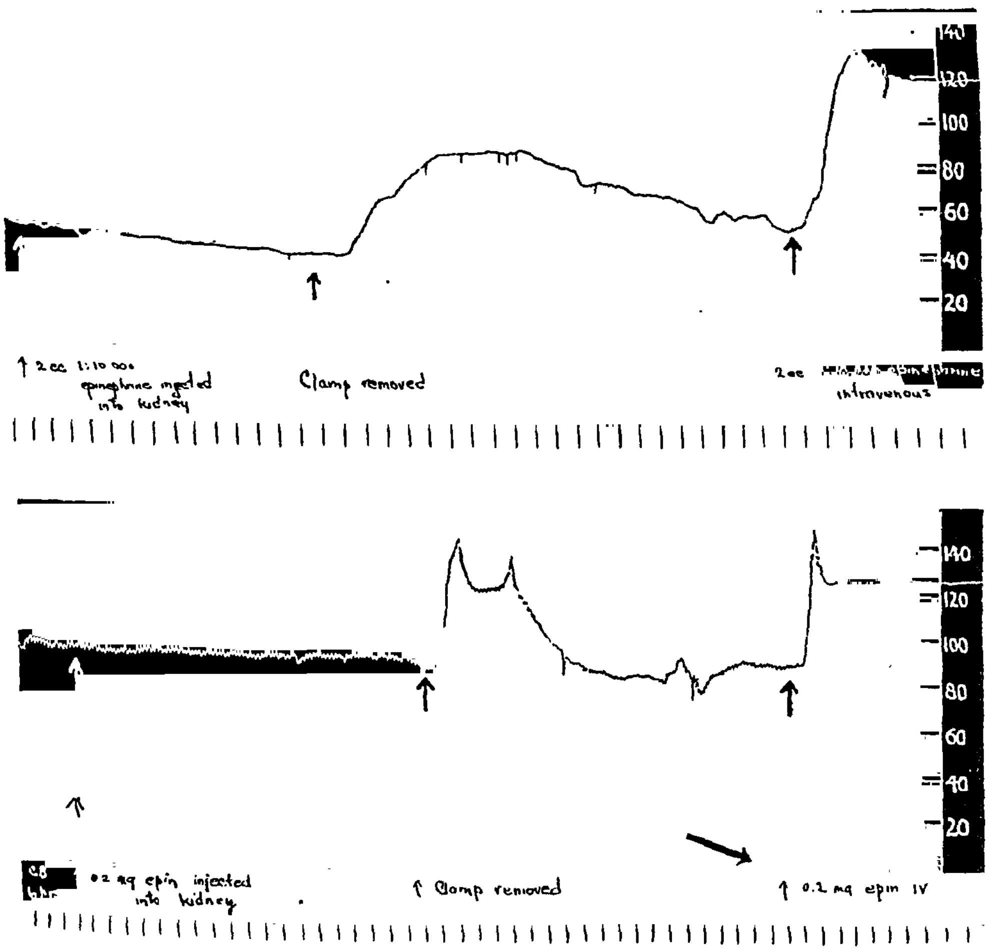

Fig. 4.—Experiments to show that renal circulation had ceased while clamp was in position and satisfactorily re-established after clamp was removed. Same animals as in Fig. 3. At first arrow, with clamp in place, 0.2 mg. epinephrine injected into kidney. No rise in blood pressure. At second arrow, clamp removed. Typical epinephrine pressor response. At third arrow, 0.2 mg. epinephrine intravenously. Similar pressor response. Nembutal anesthesia. Time marker, 15-second intervals.

pedicle by traction on the ligature leading through the abdominal wall. This procedure took no more than thirty seconds, and caused no discomfort to the animal. Blood pressure observations were made every fifteen seconds for at least ten minutes after releasing the ligature. No rise of blood pressure was observed (Fig. 5, *B*, Table III).

TABLE III

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS. LEFT RENAL ARTERY OR PEDICLE CLAMPED. RIGHT KIDNEY REMOVED. NO ANESTHESIA UPON RELEASE OF CLAMP.

ANIMAL	PROCEDURE	TIME OCCLUDED	RISE OF B. P.	FALL OF B. P.	TESTS OF RENAL CIRCULATION	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEY	KIDNEY HEPARINIZED
CA 4	Silk ligature over whole pedicle	7 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 6	Silk ligature over whole pedicle	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 8	Silk ligature over whole pedicle	4 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 13	Rubber band about renal artery	4½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 14	Rubber band about renal artery	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 16	Rubber band about renal artery	6½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 18	Rubber band about entire pedicle	4¾ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture		
CA 20	Rubber band about entire pedicle	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture		
CA 21	Rubber band about entire pedicle	7 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 22	Rubber band about entire pedicle	5¼ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+

It was observed in many of the experiments, upon examining the kidneys during life and post mortem, that thrombi had formed in the renal veins. Obviously, such experiments had to be discarded, and, in view of the fact that thrombi could sometimes not be detected at the operation, it was deemed necessary to perform a test which would prove that the renal circulation had been satisfactorily reestablished. For this purpose, after taking the blood pressure in the ear of the unanesthetized rabbit, anesthesia with nembutal was induced, the carotid artery was

cannulated, and the blood pressure recorded on a smoked drum. The abdomen was then reopened, and 0.025 mg. of epinephrine was injected into the kidney. If a well-defined rise in blood pressure took place, it was concluded that the circulation had been adequately re-established. When thrombosis had developed, the blood pressure rose slightly, or not at all, in response to the injection of epinephrine.

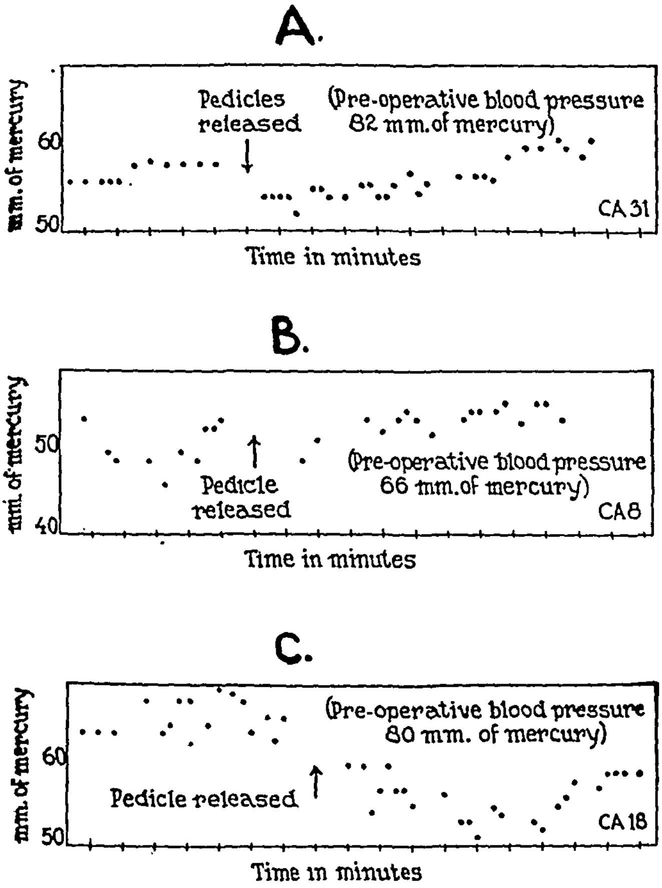

Fig. 5.—Effect on blood pressure of re-establishment of renal circulation in unanesthetized rabbits. *A*, Both renal pedicles clamped. *B*, Left renal pedicle clamped. Right kidney removed. *C*, Same as *B*, except for injection of heparin into renal artery to prevent clot formation. No rise of blood pressure in any case after release of clamp.

In almost all instances, whether or not the injection of epinephrine was followed by a pronounced rise in blood pressure, the kidneys usually assumed a distinctly abnormal aspect, i.e., they became edematous, congested, and hemorrhagic. It was thought that these abnormalities might be caused by thrombosis of some of the smaller vessels, and, for this reason, the following supplementary experiments were performed on four rabbits. The abdomen was opened under ether anesthesia, and the right kidney removed as before. The left kidney was freed of all its attachments except the pedicle, and the renal artery and vein were carefully separated. A loose ligature was placed about the renal artery in such a way that traction would occlude the vessel. While traction was thus maintained on the ligature, a small needle was introduced

into the arterial lumen close to the kidney, and a bulldog clamp placed across the renal vein. A solution of 50 mg. of heparin in 0.6 c.c. of physiologic salt solution was then quickly injected into the artery, the clamp was shifted so that it would occlude the entire pedicle, and the arterial ligature and needle were removed. Successful injection of the heparin into the lumen of the artery was signalized by immediate blanching of the cortex. The lubricated rubber band which had previously been placed loosely about the pedicle was tightened externally from the loin until the vessels were occluded; the bulldog clamp was removed, and the rest of the procedure was the same as in the experiments on nonheparinized kidneys. The animal was then allowed to recover from the anesthetic, and the experiment was completed in the manner described above. No elevation of blood pressure resulted (Fig. 5, *C*, Table III).

A third series of experiments was performed. These were similar in every detail to those of the second series, except that the pedicles of both kidneys were clamped. Four such experiments were performed; the criteria of success were the same as those previously described. (See Fig. 5, *A*, and Table IV.)

TABLE IV

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS, BOTH PEDICLES CLAMPED. NO ANESTHESIA UPON RELEASE OF CLAMP

ANIMAL	PROCEDURE	RISE OF B. P.	FALL OF B. P.	TESTS OF RENAL CIRCULATION	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEYS
CA 23	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+
CA 27	Bilateral occlusion	0	0	Vein, artery, and cortex bled	
CA 30	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+
CA 31	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+

RESULTS

In no instance did a rise in blood pressure take place in any of the three series of experiments. (See Figs. 3 and 5, and Tables II, III, and IV.)

DISCUSSION

In view of the positive results with dogs and cats,[1, 9] it is difficult to explain the failure to obtain pressor effects in these experiments on rabbits. The most logical explanation appears to be that there is a species difference, but the reasons for this difference are not easy to

comprehend because of the fact that the hypertension in all three experimental animals appears to be identical. Although it is quite clear that the mechanism of the hypertension in dogs is humoral rather than vasomotor, it seems probable that this is true also of the rabbit, for Pickering and one of us[10] found that the blood flow in the ears of hypertensive rabbits is not increased by depriving the blood vessels of their nerve supply, as would be the case if the hypertension were of vasomotor origin.

CONCLUSIONS

1. A new technique for establishing an intima-to-intima anastomosis is described.

2. Transplantation of the ischemic kidneys of hypertensive rabbits into normal animals was performed six times, and into nephrectomized animals with normal blood pressure five times.

3. In no instance was there a significant change in the blood pressure following the transplantation.

4. Complete ischemia of one kidney (after the opposite kidney had been extirpated) was produced in two series of experiments on rabbits by clamping the renal pedicle. In the first series, seven animals were anesthetized with nembutal; in the second series, six animals were unanesthetized. In a third series of four unanesthetized animals, unilateral nephrectomy was not performed, and both kidneys were made ischemic by clamping the renal pedicles.

5. In none of the seventeen animals in these three series of experiments did a rise in blood pressure occur after the clamps on the pedicle or pedicles were released.

6. In a supplementary series of four experiments, heparin was injected into the renal artery to prevent clotting during the period of total ischemia. When the clamp was released, there was no rise in blood pressure.

7. The difference between the response of rabbits and that of dogs and cats is probably an example of species variation.

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THE ROLE OF THE ARTERIOVENOUS ANASTOMOSIS IN PERIPHERAL VASCULAR DISEASE

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INTRODUCTION

Many years ago, anatomists (Sucquet,[1] in 1862, and Hoyer,[2] in 1877) called attention to the presence of direct connections between the arterioles and venules just before these vessels enter the capillary bed. Their widespread distribution over many surface areas, especially of the fingers and toes, and in internal organs as well, has since been repeatedly demonstrated.[3, 4, 5, 6] The best and most comprehensive review of the literature, to date, is that of Clark, published in 1938.[7]

For all practical purposes, however, it is only since the minute and careful histopathologic studies of Masson[8] and Popoff,[9] and the clinical work of Lewis and his school, that sufficient interest has been aroused to bring the arteriovenous anastomosis out of the dustbin of anatomic curiosities. Masson, in his classic papers, focused interest on the relationship of the arteriovenous anastomoses to so-called "glomus tumors." Popoff demonstrated their importance in various other pathologic conditions, especially inflammations and diseases of the blood vessels. Although he describes in great detail the histologic changes produced in the glomus* by arteriosclerosis and thromboangiitis obliterans, the point he stresses is that these diseases eventually turn the anastomosis from an active, contractile vessel into a permanently patent channel through which blood flows uncontrolled, directly into the venules. To obtain chemical proof of this assertion, he studied the blood gases in one case of thromboangiitis obliterans. The oxygen content of venous blood from the affected foot was definitely higher than that from the arm. Only the shunting of unused arterial blood, in his opinion, could explain this difference.

It was our purpose to investigate the role of the arteriovenous anastomosis in peripheral vascular disease by thoroughly examining the blood for its content of certain metabolites. Since these substances are either produced or consumed locally, the results may be considered a measure of the efficiency of the local blood supply.

METHOD OF STUDY

Goldschmidt and Light[10] and Looney and Childs[11] have shown that the composition of the blood gases is greatly influenced by various physical factors. However,

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*Glomus, as used by Popoff, includes not only the anastomosis, but also the afferent arteriole, collecting system of veins, and the surrounding neuromuscular network.

standardization of procedure and a knowledge of the accuracy and limitations of the analytical methods which we employed enable us to attach significance to our comparative results.

The patient was kept at complete rest for at least one-half hour, about three to four hours after a light morning meal. His arm and leg were kept uncovered and dependent, and the room temperature was maintained between 69° and 72° F. Blood was withdrawn, without using a tourniquet, from a prominent antecubital vein or from the vein behind the malleolus at the ankle. The syringe in which it was collected contained a thick layer of mineral oil, and the tube in which it was stored, under anaerobic conditions, contained a column of oil at least 2 inches thick. Analysis of the blood samples was done immediately, in duplicate. The results of the two analyses usually differed no more than 0.2 to 0.3 volume per cent. If the difference exceeded 0.5 volume per cent, a third analysis was made.

The oxygen content, oxygen capacity, carbon dioxide content, and lactic acid content of the blood were ascertained by the gasometric methods of Van Slyke and Peters.[12]

Although glucose, urea nitrogen, nonprotein nitrogen content, and carbon dioxide combining power were ascertained in many cases, the results obtained were so inconstant and inconclusive that further study of these substances was abandoned.

COMPARISON OF ARM AND FOOT BLOOD

In this first group of experiments, blood from a region with an adequate (checked by the usual methods) circulation—the arms—was compared with that from a region with greatly impaired circulation—the lower extremities. Nearly all of the patients had advanced peripheral arteriosclerosis; a few had thromboangiitis obliterans. They were all patients whose vascular disease had been present for years, and all gave the usual history of intermittent claudication, or pain at rest. Typical rubor, pallor, and dependent cyanosis were present. Pulsations in the vessels of the lower extremity were very feeble or absent; this was substantiated by oscillometric readings. In all cases the skin temperature of the legs was lower (3° to 11° F.) than that of the arms. Many of the patients had diabetes, and in one or two cases the vascular disease was complicated by peripheral neuritis.

TABLE I

COMPARISON OF FOREARM AND FOOT BLOOD IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	ARM	FOOT	ARM	FOOT	ARM	FOOT	ARM	FOOT
1	15.2	18.7	52.0	49.9	14.2	17.7		
2	18.0	20.2	52.8	52.0	10.0	15.1		
3	9.8	18.1	53.8	48.3	12.5	13.9		
4	16.3	18.1	50.0	49.7	16.7	18.0		
5	11.4	19.5	50.0	44.3	15.6	17.2		
6	10.5	12.6	51.8	50.4	14.1	14.5		
7	16.4	17.8	49.4	46.9	12.7	13.9	19.2	18.5
8	6.9	12.8	55.8	51.2	11.6	22.3	18.5	18.1
9	12.6	18.9	54.9	49.9	12.8	15.1	21.7	21.7
10	9.7	12.3	55.8	56.3	9.5	9.5	20.7	20.7
11	13.7	16.1	58.3	57.1	18.0	19.5	23.3	18.7
12	16.7	18.9	46.7	43.7	11.6	17.7	21.6	22.1
13	10.5	11.2	52.8	51.1	11.4	13.4	19.4	20.8
14	13.3	13.3	56.0	54.7	13.9	16.5	17.0	17.9
15	17.0	17.0	51.5	52.7	14.2	15.0	19.4	20.5

The results are presented in Table I. The oxygen content of the venous blood from the lower extremities in thirteen of the fifteen cases of peripheral vascular disease was significantly higher than that from the forearms. This is all the more surprising because, as has been noted, pain, cyanosis, and the cold, clammy skin of the involved extremities indicated how inadequate was the peripheral circulation, and how precarious was the prognosis for that limb. In the other cases, the oxygen content of arm and foot blood was identical.

The difference in oxygen content varied from 0.7 volume per cent to 8.3 volumes per cent. The highest values, curiously enough, were obtained in certain cases in which the disease was farthest advanced. The fact that the oxygen capacity of the blood was practically constant indicates quite conclusively that the disparity in the oxygen content of the arm and foot blood was the result of a difference in arterialization, not in concentration of hemoglobin.

TABLE II

COMPARISON OF FOREARM AND FOOT BLOOD IN NORMAL PEOPLE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	ARM	FOOT	ARM	FOOT	ARM	FOOT	ARM	FOOT
1	17.7	16.9	47.5	46.0	16.0	15.8		
2	18.8	17.0	51.4	51.2	15.9	14.1		
3	11.8	14.4	53.5	52.0	14.8	15.0		
4	16.7	17.4	46.9	43.0	10.1	12.0		
5	15.7	15.4	49.2	49.2	14.5	14.5	20.5	20.4
6	12.4	14.9	53.0	50.0	11.0	16.5	21.0	21.2
7	16.8	13.2	51.2	51.8	12.6	13.5	20.2	20.0
8	18.3	17.8	49.9	50.5	11.8	12.1	21.0	21.1
9	17.2	16.6	53.2	53.0	19.7	19.7	19.1	19.0
10	11.5	12.2	50.8	50.3	18.6	17.8	18.2	18.9
11	14.0	16.0	52.7	51.4	10.1	11.5	17.1	18.5
12	12.1	11.5	58.1	50.9	14.4	14.8	18.0	17.5
13	14.2	11.0	52.8	53.2	8.6	8.6	16.3	16.7
14	8.2	7.1	62.6	63.0	15.6	15.5	19.4	20.1
15	18.0	14.5	51.6	51.4	9.0	11.9	20.7	20.6

In sharp contrast were the values found in a group of normal adults who were used as *controls* (Table II). There was no definite trend; in five cases the oxygen content of the foot blood was slightly higher, in five other cases the values were essentially the same, and in the remaining five the oxygen content of the foot blood was lower than that of the arm blood. Such differences are to be expected and are an index of the variability of response of normal persons to the same physiologic conditions. They do serve the purpose of emphasizing still further the significance of the results obtained in the first group.

As was to be expected, the values for the carbon dioxide content varied, in general, in the opposite direction to those for oxygen. In a number of cases, however, the differences in the carbon dioxide content of the venous blood from the arm and foot were not as marked as were the disparities between the oxygen values.

There were changes in the other constituents of the peripheral blood, but they were of the same degree and in the same direction in both groups, so that generalizations cannot be drawn. A remark must be made about the values for lactic acid in the venous blood from the diseased extremities. These showed a definite tendency to be near the upper limit of normal, or even above normal.

EFFECT OF EXERCISE

In the next series of experiments, twelve patients with peripheral vascular disease were used. Samples of blood from the lower extremity were first obtained in the usual manner. Then each subject was made to extend and flex the toes, slowly, but forcefully, twenty times. The needle was kept in the vein during this time, and, towards the end of the exercise period, another blood sample was collected.

TABLE III

EFFECT OF EXERCISE IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE
1	11.6	8.2	51.6	55.8	20.0	26.7		
2	15.6	8.7	50.8	56.6	29.8	35.3		
3	15.8	8.5	54.9	58.1	19.1	32.7	21.4	21.4
4	20.8	12.7	46.8	56.5	18.3	25.3		
5	10.6	8.2	48.2	55.5	18.1	24.4	20.2	19.6
6	18.3	17.4	48.8	49.4	12.1	19.5	18.9	18.9
7	14.3	9.2	54.4	57.7	16.7	22.5	17.5	17.4
8	14.4	14.2	55.8	58.5	17.9	18.5		
9	13.5	14.8	56.4	58.8	22.2	37.4		
10	8.4	9.4	64.3		23.8	34.8		
11	9.2	10.4	49.4	49.4	18.1	24.4	19.4	19.5
12	9.3	10.8	56.8	58.2	35.0	63.0	21.9	21.8

The most constant result of exercise was a pronounced rise of lactic acid above the basic level, which was already a high normal, or even above normal. Only in this respect did the results differ from what ordinarily occurs in normal subjects after exercise.

In eight cases, a drop in the oxygen content coincided with the exercise. Utilization of oxygen during the performance of work, is, of course, to be expected. Of more significance, however, was the fact that in four cases there was, instead of this expected result, a slight but distinct rise in the oxygen content of the peripheral blood. This rise was coupled with a marked elevation of the lactic acid content. The significance of these changes will be made clear later.

RECOVERY AFTER EXERCISE

In a third, and final, group of experiments, ten patients with peripheral vascular disease were made to exercise as before, i.e., contract the toes, slowly and forcefully, twenty times. Samples of blood from the same ankle vein were withdrawn immediately after the exercise, and

again following a rest period of one-half to one hour. During this interval, the foot was kept relaxed and in a dependent position.

TABLE IV

RECOVERY AFTER EXERCISE IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST
1	8.0	13.6	49.6	42.8	22.7	13.5	15.5	15.6
2	13.8	18.2	49.7	44.8	43.0	34.0	19.9	19.7
3	6.5	11.8	59.5	55.2	33.0	18.5	21.6	22.2
4	7.2	10.9	56.6	50.2	41.1	25.1	17.4	17.8
5	12.6	13.5	50.7	51.8	12.1	10.3	16.5	16.5
6	13.3	16.3	58.6	49.4	24.0	15.0		
7	13.3	20.1	63.8	51.9	19.7	14.6		
8	11.2	10.1	51.2	50.6	31.7	22.0		
9	9.0	9.9	61.5	57.3	52.5	36.5		
10	15.9	18.5	42.5	40.0	47.5	52.5		

The results (Table IV) parallel those in normal subjects who are recovering from fatigue. The oxygen deficit tends to disappear, and carbon dioxide and lactic acid values tend to return to their usual resting levels. There is, however, one important difference, namely, the time element. In many instances there were still an oxygen deficit and a high lactic acid level at the end of a test period of one-half, or even one hour, which is usually sufficient time for complete restitution in normal subjects. The inadequacy of the peripheral circulation was again demonstrated.

DISCUSSION

The fact that the arteriovenous anastomoses help to maintain the surface temperature of animals has been known for many years. Only recently did it become evident, through the studies of Grant and Bland[13] and Lewis and Pickering,[14] that they perform the same function in man.

The presence of active, contractile, comparatively large channels, which, like safety valves, permit rapid shifting or shunting of blood from the tissues directly into the venules is, of course, quite physiologic when the vascular tree is elastic and ample for tissue requirements; but in a region which has already been deprived of much of its vascular supply by disease processes, such a shunt can serve no useful purpose and may actually constitute a menace to the life of that part. Arterial blood laden with nutritive substances which are urgently needed by the tissues is sidetracked and returned to the general circulation without fulfilling its function.

Our experiments show that, at rest, the venous blood from a foot with impaired circulation carries more oxygen and frequently less carbon dioxide than the venous blood from the forearm. This is combined with a relatively high lactic acid content.

In the presence of peripheral vascular disease, the relatively high oxygen and low carbon dioxide values cannot be the result of increased

blood flow through the tissues. The constancy of the oxygen capacity shows that these abnormalities cannot be caused by an increase in blood concentration. They might be produced by a diminished permeability of the capillaries. However, we would then expect to find a low lactic acid concentration in the venous blood, and the capillaries should carry arterial blood throughout, i.e., the skin should have a bright red color.

We must therefore assume, as did Popoff, that, in peripheral vascular disease, patency of the arteriovenous anastomoses, even at rest, permits arteriovenous shunting of blood to play a major role in the peripheral circulation.

Under the influence of local muscular exercise, this shunting of blood is apparently reduced in many cases. Such patients respond to light exercise with utilization of blood oxygen and an accumulation of lactic acid. During the period of recovery, the local blood supply to the tissues was, in some instances, sufficient for a complete return to normal. In other cases, however, after the rest period, the venous blood still showed an oxygen deficit and a high lactic acid content. Occasionally, patency of the arteriovenous anastomoses was maintained during exercise, at a time when the demand for capillary circulation was very urgent. The "shunt" was manifested by an increase in oxygen content; insufficiency of the capillary circulation, by a marked accumulation of lactic acid.

It is apparent, therefore, that knowledge of the total blood flow through a given area, such as is obtained from plethysmographic studies, may be of little aid in estimating the efficiency of the local circulation. In certain cases only part of this blood passes through the capillaries and is available for utilization by the tissues. The remainder, which is shunted directly from arteriole to venule, is useful mainly in maintaining the local temperature. Although, according to Wright and Duryee,[15] there is some exchange of tissue fluid through the highly permeable venule walls, tissue metabolism depends essentially on capillary circulation. "Shunt" circulation, for practical purposes, is a loss as far as tissue metabolism is concerned.

This concept is important if we are to formulate a sound approach to the therapy of peripheral vascular disease. The ultimate purpose of all treatment must be improvement of the blood supply to the tissue proper.

SUMMARY

1. A relatively high oxygen and low carbon content of the venous blood from a region with impaired circulation, together with a relatively high lactic acid content, points to the presence of patent arteriovenous anastomoses.

2. Exercising an extremity in which the circulation is impaired produces either the usual chemical effect of fatigue, or, if a "shunt" circulation dominates, an increase in oxygen, together with an accumulation of lactic acid, in the venous blood.

3. The efficiency of the peripheral circulation in the presence of vascular disease of the extremities depends upon the flow of blood through the available capillary bed. Increased blood flow through an extremity when the arteriovenous anastomoses are patent does not necessarily mean that the capillary circulation to the tissues is augmented.

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CARDIAC HYPERTROPHY CAUSED BY GLYCOGEN STORAGE DISEASE IN A FIFTEEN-YEAR-OLD BOY

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A CASE of abnormal glycogen deposition in a 15-year-old boy with extreme cardiomegaly was encountered. It differed somewhat from the classical cardiomegalic type of von Gierke's disease,[1-9] but, nevertheless, illustrated many of the cardinal features of this disorder of glycogen metabolism.

REPORT OF CASES

CASE 1.—*First admission*, Aug. 10, 1936; discharged, Aug. 28, 1936. A. H., a 15-year-old, Jewish schoolboy, entered the Mount Sinai Hospital because of progressively increasing dyspnea on exertion for the preceding two years. He had been "below par" for three years, as evidenced by his poor appetite, pallor, and fatigability. Three years before, he had experienced transient pain in his joints. Four years earlier, a teleoroentgenogram had shown a "bad heart."

Physical Examination.—The patient was a fairly well-developed and well-nourished white boy who was slightly dyspneic and orthopneic.

There was flatness to percussion at the extreme bases of both lungs posteriorly and in the axillae, with diminished intensity of the breath and voice sounds and absent fremitus. No râles were heard. The bases were not fixed.

The heart was markedly enlarged to the left. A short, blowing, systolic murmur was heard over the entire precordium. The rate was rapid and the beating was regular; gallop rhythm was audible over the entire precordium. The blood pressure was 120/80. The liver extended 1½ fingerbreadths below the costal margin, and was not tender.

Laboratory Examination.—The urine showed a trace of albumin on admission, but was negative thereafter. Acetone was tested for but not found. The hemoglobin was 100 per cent, the leucocyte count, 11,800, and the differential count, normal. The sedimentation time of the erythrocytes was four hours. The urea nitrogen content of the blood was 13 mg. per cent, the cholesterol content, 210 mg. per cent, the esterified cholesterol content, 65 mg. per cent, and the sugar content, 105 mg. per cent. The icteric index was 16. The blood Wassermann reaction was negative. The electrocardiogram revealed sinus tachycardia and an atypical, left-sided, bundle branch block.

Roentgenologic examination of the chest revealed a generalized enlargement of the heart, particularly of the left ventricle, which was both hypertrophied and dilated. There was enlargement of the left auricle, with elevation of the left main bronchus, giving the appearance of a combined mitral and aortic lesion. Slight pulmonary congestion was evident.

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Course and Diagnosis.—The congestive heart failure was quickly relieved by rest in bed, mercupurin, and digitalis. The gallop rhythm also disappeared. The cause of the hypertrophy remained obscure. Congenital heart disease was eliminated because of the absence of characteristic murmurs, cyanosis, and confirmatory roentgenologic observations. The fact that there was no definite history of rheumatic fever, together with the absence of characteristic murmurs, made it unlikely that this was a case of rheumatic valvulitis. Two other possible causes of the hypertrophy, namely, chronic interstitial myocarditis (Fiedler's myocarditis) and von Gierke's disease, were considered. In the absence of hypoglycemia and acetonuria and of excessive enlargement of the liver and kidneys beyond that which might be expected in cardiac insufficiency, and because of the age of the patient, the possibility of von Gierke's disease was clinically ruled out. In view of all of the above considerations, a diagnosis of cardiac hypertrophy of unknown cause was made.

Second admission, Oct. 1, 1936; died, Nov. 7, 1936. After his discharge from the hospital, the patient had been free from all symptoms, except dyspnea on exertion, until one week before readmission, when he felt feverish and coughed up small amounts of non-foul-smelling sputum. Following this, he developed fever and a persistent cough, and occasionally vomited.

Physical examination revealed essentially the same abnormalities as on the first admission. The arterial pressure measured 140/92 mm. Hg, and the venous pressure, 15 cm. of water. There was slight pretibial edema.

The results of the laboratory examination did not vary from those on the first admission, except that the fasting blood sugar content was 70 mg. per cent, the cholesterol content, 155 mg. per cent, and the esterified cholesterol content, only a trace. The electrocardiogram was essentially the same as on the first admission.

During the patient's stay in the hospital he had a persistent fever of 101° which was attributed to chronic sinusitis. The blood culture remained sterile. Four weeks after admission the spleen became palpable. Because of this and the fever, the possibility of active myocarditis was entertained. The vital capacity was diminished to 1900 c.c. The saccharin circulation time was prolonged to forty-five seconds. Five and one-half weeks after admission there was an increasing degree of congestive heart failure, and the patient died in his sleep.

Necropsy.—(10127.) Necropsy was performed twelve hours after death.

The body was that of a well-developed white boy, 15 years of age, in complete rigor mortis. There was edema of the ankles.

Abdomen.—The peritoneal cavity contained a small quantity of turbid fluid. The mesentery was edematous. The liver extended 4 cm. below the costal margin in the midclavicular line. The spleen did not project beyond the costal margin.

Thorax.—The heart was universally enlarged (Fig. 1), and, together with the root of the aorta, weighed 650 grams (average normal, 247.5). Chemical studies revealed that the glycogen content of the heart muscle was 4 per cent, despite the fact that the necropsy was performed twelve hours after death. The heart displaced both lungs in such a way that each was compressed into the lateral and posterior hemithorax, particularly on the left side. The pleurol cavities were normal. The right auricular appendage was dilated. The atrium had a distinctly thickened wall, and the endocardium was opaque. The foramen ovale was closed. The septal leaflet of the tricuspid valve was slightly thickened. The right ventricular wall was 1 cm. thick. The septal portion bulged into this ventricular chamber, narrowing the cavity. The endocardium was translucent. The underlying myocardium had a homogeneous, pale, yellow-brown color. The outflow tract of the right ventricle was markedly hypertrophied, and bulged into the ventricular lumen. The pulmonary cusps showed no significant changes. The width of the pulmonary artery just above the free margin of the cusps was 7.5 c.mm. (average normal, 5.9).[10] The

pulmonary artery showed nothing unusual. The endocardium of the left auricle was uniformly thickened and opaque, and, in places, finely wrinkled. There was no evidence of a MacCallum lesion. There was a fine, ridgelike thickening along a short area of the free margin of the posterior leaflet of the mitral valve, together with slight, irregular thickening of a few chordae tendineae. No vessels could be detected in the valve. The left ventricular wall was considerably thickened; it measured 1.8 cm. in its midportion. On section, the musculature was reddish gray. The chamber was elongated and markedly dilated. The endocardium was irregularly thickened, grayish, and opaque, especially in the outflow tract. There were no regurgitation pockets. Irregularly distributed areas of purple coloration were seen in the anterior papillary muscle, the posterior wall of the ventricle, and the upper, anterior portion of the interventricular septum. The aortic cusps showed no significant changes. The commissure between the posterior and left anterior cusps was slightly fused. The coronary vessels were patent throughout their course. The aortic valve measured 5.1 cm. across (average *normal*, 5.42).

Fig. 1.—Heart showing hypertrophy of the left and right ventricles.

The circumference of the aorta at the beginning of the descending thoracic portion was 4.2 cm. (normal, 4.3), and, at the branching of the coeliac axis, 3.5 cm. (normal 3.84 at diaphragm). The aorta was elastic. The intima was smooth except for a few, small, slightly raised, yellow plaques in the descending thoracic portion.

Lungs.—The lungs were markedly congested. There were small hemorrhagic infarcts in the right upper and left lower lobes. On the left there was a middle lobe whose shape and bronchial supply corresponded to those of the right middle lobe. The pulmonary vessels were not unusual.

Liver.—The liver weighed 1850 grams. It was firm, large, and had a rounded edge. The surface was smooth and deep purple. The cut surface had a distinct brown appearance. The architecture was well discernible. The central zones of the lobules were seen as fine, red dots and streaks. The hepatic vessels and portal vein showed no gross abnormalities.

Spleen.—The spleen was very firm and congested, and weighed 470 grams. The follicles were large and prominent.

Kidneys.—The kidneys were red-brown and firm, and, together, weighed 380 grams. No gross changes were observed.

Lymph Nodes.—The intra-abdominal and intrathoracic lymph nodes were slightly enlarged and moderately firm.

Sections of all organs were fixed in absolute alcohol and formalin for histologic study. The weighed portions were minced and placed in acetone, alcohol, and glycerine for chemical studies.

Histologic Changes.—Heart: The most conspicuous changes were found in the left ventricular myocardium. The right ventricle was similarly involved, but to a lesser extent. With the hematoxylin and eosin stain, in paraffin sections, most of the muscle fibers were found to contain an elongated, irregularly outlined, elliptical area which was either empty or filled with a very delicate basophilic or slightly eosinophilic network. In places, the vacuoles in the central zones of the muscle fiber were so pronounced that only a thin, cylindrical shell of muscle substance (sarcoplasm) could be seen on cross section. Many of these vacuolated zones also contained clumps of a homogeneous, darkly basophilic material. This has been described in only one other instance of von Gierke's disease.[9] The nuclei were mostly very large, and presented bizarre, angulated, or elongated forms, with dense, basophilic, clumped, chromatin material. Their situation within the individual fibers was variable. In places, the nuclei were found in the center of the vacuole, and were completely surrounded by it, but, for the most part, they were situated in the periphery of the vacuole, as though pushed aside (Fig. 2*A*). In scattered areas of the left ventricular wall there was a moderate proliferation of fibroblasts, and some fibers were surrounded by small collections of round cells (Fig. 2*B*), with occasional histiocytes and polymorphonuclear leucocytes. Scattered throughout the myocardium there were also foci of interstitial fibrosis (Fig. 2*D*); these were not confined to the perivascular zones.

In one place there was a marked, fibrous thickening of the wall of a small vein, which contained an organizing parietal thrombus. The small arteries showed no significant changes. The mediae of the larger arteries were moderately thickened as the result of the deposition of a homogeneous substance between the muscle bundles, but only a very few of the muscle fibers stained red with Best's carmine. The auricular endocardium was slightly thickened. There was moderate subendocardial fibrosis, with an increase in fibroblasts. The auricle was otherwise normal. The mitral valve showed slight fibrous thickening. No vessels were seen in the valve. The aortic and tricuspid valves showed no significant histologic changes. The ventricular endocardium was slightly thickened.

Sections of myocardium which were stained with Best's carmine showed large amounts of glycogen not only in the zones where vacuoles were seen in the hematoxylin-eosin preparations, but also in the intracellular basophilic bodies described above. The glycogen in the inner zones of the muscle fibers was deposited

homogeneously, and only under high magnification could one occasionally distinguish fine droplets. The endomysial cells were easily discernible. Rarely, an endomysial cell was slightly swollen, and contained small amounts of homogeneously stained glycogen.

In some places, the cross striations appeared as straight lines impregnated with glycogen; in others, the glycogen was strung along the cross striations in red droplets, like beads on a thread. This corresponds to the distribution of glycogen in control sections from comparatively normal hearts.

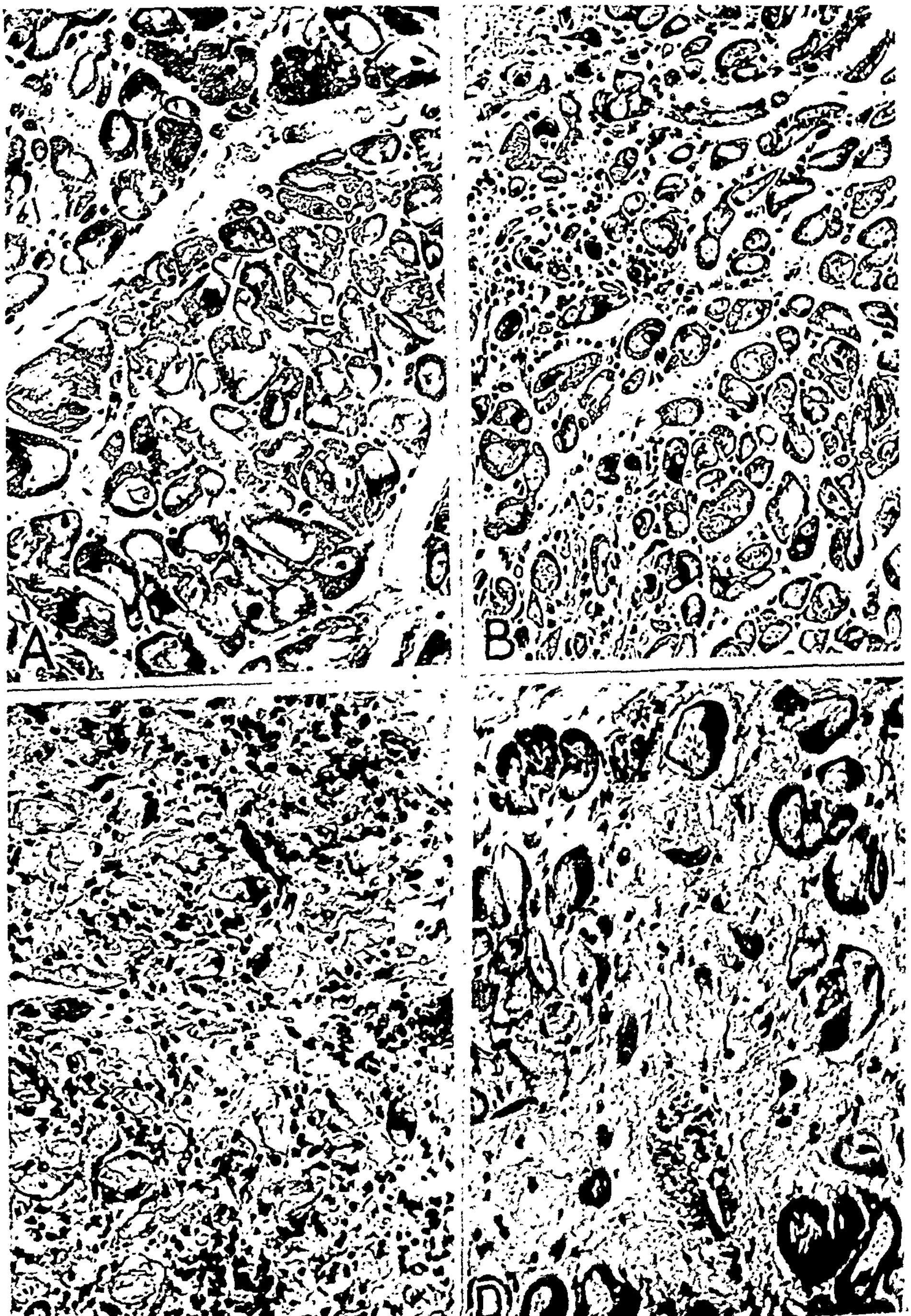

Fig. 2.—Hematoxylin and eosin stain of, *A*, vacuolated myocardial fibers. Some of the nuclei are compressed. *B*, Vacuolated myocardial fibers. Interstitial collections of round cells. *C*, Degenerated and necrotic myocardial fibers with inflammatory reaction. *D*, Myocardium with areas of fibrosis. (×175.)

Interventricular Septum.—The general appearance was similar to that of the left ventricular wall, except that the inflammatory lesion was more severe. A broad area beneath the left ventricular endocardium, particularly in the uppermost portion, was the seat of very conspicuous infiltration. In large, irregularly outlined areas, the myocardium was replaced by a highly vascularized, and in places, hyalinized, connective tissue. In its meshes were fragments of degenerating muscle fibers, with indistinct striations, which retained their large, pyknotic nuclei. Most of the fibers were filled with glycogen, so that only a very thin mantle of sarcoplasm remained about the masses which contained basophilic glycogen. About these degenerating muscle fibers there was a severe inflammatory reaction, with numerous, large histiocytes, lymphocytes, and scattered polymorphonuclear leucocytes (Fig. 2C). No plasma cells were noted. In many instances the inflammatory cells surrounded, and appeared to be attacking, single, degenerating muscle fibers. Free masses of glycogen were also found. Large numbers of phagocytes were laden with glycogen. In areas of very dense cellular infiltration, the proportion of polymorphonuclear leucocytes was greater than in the remaining tissue.

We failed, as did Putschar,[2] Humphreys and Kato,[8] and Wolff,[9] to differentiate histologically the fibers of the conduction system from the remainder of the glycogen-laden heart muscle fibers, although serial sections were studied in the region of the bundle of His. Histologic examination of the bundle region showed an extensive inflammatory reaction. The electrocardiogram in this case revealed bundle branch block, indicating an involvement of the conduction system.

Peripheral Muscle (Psoas).—The muscle fibers were very broad, and showed many central vacuoles and masses. These also gave a positive glycogen reaction. The nuclei were in their normal peripheral position. The sarcolemma cells were swollen, and contained considerable amounts of glycogen; thus, the sarcolemma formed a peripheral coat around the muscle fiber (Fig. 3*B*). In many places the granular deposits in the fibers were so massive that only scattered fragments of fibers and a mantle of endomysium remained. The degenerated muscle fibers were surrounded by round cells, histiocytes, and, occasionally, polymorphonuclear leucocytes (Fig. 3*A*). A great number of glycogen-containing phagocytes were noted within the endomysium. The phagocytic action of these cells has been stressed by Maximow and Bloom.[30]

Muscle From the Neck.—The fibers were normal, and there were small amounts of glycogen. In only a few fibers was the glycogen centrally located.

Tongue.—The musculature did not show any significant changes. In a few areas, muscle fibers were surrounded by thin sheaths of glycogen which, apparently, was deposited in sarcolemma cells.

Diaphragm.—The glycogen deposition was similar to that in the psoas muscle, but there was much less of it.

Esophagus.—The striated muscle fibrils did not take the glycogen stain. In the smooth muscle, however, there were numerous fibers which contained homogeneous masses of glycogen; in some places these were basophilic.

Smooth Muscle.—Examination of the smooth musculature throughout the body showed that there was a considerable amount of homogeneous glycogen in single muscle fibers. It was basophilic in many places. Large deposits were noted in the fibers of the *bronchial musculature* and in the muscle of the *epididymis.* Moderate amounts were present in the musculature of the *bladder, prostate,* and many *arteries* and *veins.* This was demonstrated in the carotid artery, vessels of the adrenal, and arteries and veins in the lungs, gall bladder, and epididymis. In hematoxylin-eosin preparations, the areas corresponding to the glycogen were often basophilic.

Liver.—There was marked chronic passive congestion. The central liver cells contained large amounts of lipofuscin and fat. There were marked congestion and edema in the Desse spaces. The Kupffer cells were not prominent. The portal fields showed moderate infiltration with round cells and a few polymorphonuclear leucocytes. The hematoxylin-eosin stain showed that numerous liver cells had a pale, eosinophilic, foamy cytoplasm and a basophilic rim. The nucleus was displaced to the periphery. Best's carmine stained these cells intensely red; the remainder of the liver cells showed glycogen granules only along their borders. In general, there was a fairly large amount of glycogen, but this did not exceed the amounts found histologically in some control slides. The deposited glycogen granules, however, appeared coarser than those in the control livers.

Fig. 3.—*A*, Hematoxylin and eosin stain. Psoas muscle with basophilic masses in fibers and interstitial collections of round cells. *B*, Best carmine stain. Glycogen in sarcolemma and in muscle fibers. (×258.)

Lungs.—The histologic changes were those of chronic passive congestion. A section from the left lower lobe showed an organizing arterial embolus and hemorrhagic infarction.

Spleen.—Sinus hyperplasia was prominent. The follicles were well outlined.

Kidney.—There was marked congestion. Bowman's spaces contained coagulated plasma and a few erythrocytes. The tubules were degenerated, and contained very small amounts of fat. No glycogen was found within the renal epithelium.

Stomach and Intestinal Tract.—There were only sporadic glycogen-containing muscle fibrils. The pyloric musculature was free from glycogen.

Sections of the thyroid, lymph nodes, bone marrow, peripheral nerves, sympathetic ganglia, adrenals, brain, pituitary, and pancreas showed no significant changes.

Inasmuch as von Gierke's disease has been reported in siblings,[31, 33, 34] the case of A. H.'s 11-year-old brother, which was very similar, is also presented.

CASE 2.—This boy was admitted to the Mount Sinai Hospital March 31, 1937, with a complaint of shortness of breath and pallor of five weeks' duration. One brother (A. H., Case 1) had died at the Mount Sinai Hospital, four months earlier, of glycogen storage disease which chiefly involved the heart muscle; one other brother was living and well. The patient had always tended to be obese, and had been on a reducing diet several times.

His illness had probably started several months before admission, at which time he complained of shortness of breath and palpitation on climbing stairs. Five weeks before admission, the patient had an upper respiratory infection, with a temperature of 101 to 102° F. His mother stated that he was uncomfortable, and that his respirations were rapid when he was in the recumbent position. The dyspnea increased rapidly, and immediate hospitalization was advised because he was thought to have "pericarditis." At another hospital he was given oxygen through an intranasal catheter for three days, which relieved his dyspnea somewhat. After one week in the hospital, the patient was taken home against advice. In the week preceding his admission to the Mount Sinai Hospital, the anorexia, nausea, vomiting, dyspnea, and orthopnea continued. It was noted that the legs had become swollen in the dependent portions. The urinary output had diminished. On the day of admission the patient was irrational and delirious.

Physical Examination.—The temperature was 98.8° F., the pulse rate, 112, and the respiratory rate, 34. The patient appeared to be both acutely and chronically ill; he was pale, looked tired, and had moderate dyspnea and orthopnea. The skin was cool, dry, and rough. The precordium bulged slightly. There were dullness to percussion and diminished intensity of the breath sounds at the base of the right lung. The point of maximum impulse was felt in the fifth intercostal space in the anterior axillary line; percussion showed that the heart was enlarged to the right and left; the left border was near the anterior axillary line. The heart rate was rapid and the sounds were faint; the pulmonic second sound was louder than the aortic, and there was a moderately loud systolic murmur over the apex which was transmitted upward and outward. The systolic blood pressure was 90; the diastolic could not be measured. The liver was palpable 6 cm. below the costal margin in the midclavicular line. Both flanks bulged slightly.

It was our impression, on admission, that the patient had von Gierke's disease, with myocardial failure. A teleoroentgenogram showed marked enlargement of the heart to the left and right.

Laboratory Examination.—The urea nitrogen content of the blood was 10 mg. per cent. The Janney test gave the following result: 70, 85, 115, 110, and 95. The

chloride content of the blood was 510 mg. per cent, the phosphorus content, 3.75 mg. per cent, and the calcium content, 7.8 mg. per cent. The Takata-Ara test was negative. The blood Wassermann reaction was negative. The icteric index was 12. The galactose tolerance test was negative. The total protein content of the plasma was 5.7 per cent, of which albumin was 2.9, and globulin, 2.8. The cholesterol content of the blood was 185 mg. per cent, and the esterified cholesterol content, 36 mg. per cent.

The hemoglobin was 96 per cent, the erythrocyte count, 4,190,000, the leucocyte count, 22,600, and the platelet count, 195,000. The differential leucocyte count showed 83 per cent polymorphonuclears, 7 per cent juvenile cells, 9 per cent lymphocytes, and 1 per cent monocytes. Examination of the blood smear showed anisocytosis, polychromatophilia, and giant platelets. The tourniquet test was negative.

The urine was normal on several occasions, but the last specimen which was examined contained a few hyaline and granular casts; acetone was found in the urine only once while the patient was vomiting.

The electrocardiogram revealed sinus tachycardia and changes which were interpreted as indicative of left ventricular enlargement, myocardial disease, and left bundle branch block.

Course.—The patient grew progressively worse. He was afebrile on admission, but thereafter he had a low-grade fever which exceeded 100° F. on two days only. He died with the clinical manifestations of myocardial failure. Permission to perform an autopsy could not be obtained.

DISCUSSION

The outstanding features of the first case were the excessive deposits of glycogen in the heart and systemic musculature and the pronounced cardiac hypertrophy.

We believe that the patient had the cardiomegalic type of von Gierke's disease. However, because of his age, a critical consideration of other possibilities is in order, for, of the cases so far reported, none has occurred in patients beyond the age of 8 months, except possibly in the case of Fliess and Bloom, in which the patient was still alive at the age of 2 years and 4 months.[11]

The changes in certain areas of the heart muscle resembled those which are caused by coronary occlusion. It is known that, after severe myocardial ischemia, the vacuoles, as a rule, contain glycogen. The patency of the coronary arteries, the normal dimensions of the main vessels, and the absence of congenital defects exclude the possibility that mechanical interference with the blood supply was a factor in this case. It might, however, explain the localized glycogen deposition in the case of Finkelstein,[12, 20] in which the left coronary artery arose from the pulmonary artery.

The vacuolated myocardial fibers in cases of beriberi[13] simulate those which were found in the present case.[14, 15]

This case also throws further light on the relationship between some cases of idiopathic hypertrophy of the heart and von Gierke's disease.[2, 4, 5, 7, 8] The term "idiopathic hypertrophy of the heart" is used when no cause for the hypertrophy can be found.[18, 19] The cardio-

megalic form of von Gierke's disease was placed in a separate category as soon as its true nature had been established.[21] Although the existence of other etiologic factors in "idiopathic hypertrophy" cannot be denied, glycogenosis may also play a significant role in the causation of cardiac hypertrophy of obscure pathogenesis. "Idiopathic hypertrophy of the heart" occurs not only in early infancy, but also in later childhood.[18, 19, 22, 23, 24] If the cardiac manifestations of abnormalities of glycogen metabolism should be related to some of the instances of idiopathic hypertrophy, they also should occur after infancy. The arrest of glycogen storage disease without cardiac involvement has been reported in older children,[2, 5, 25, 26, 27, 29, 32] and, in some of the cases in which no cardiac enlargement was found clinically, post-mortem examination revealed the presence of large amounts of glycogen within the heart.[1, 3, 16]

It is also to be considered that, in contrast to the liver, the overfilling of the myocardium with glycogen is distinctly abnormal after infancy, and it is questionable whether, after a prolonged period of engorgement with glycogen, the myocardium can return completely to its normal functional and morphologic state. In addition, the inflammatory response to these severe, irreversible, degenerative changes, together with necrosis of the myocardium, might further hinder recuperation. The eventual, composite picture would consist, therefore, of normal areas, areas in which the myocardial fibers harbored an abundance of glycogen, areas of inflammation (Fig. 2*B* and *C*), and areas of fibrosis (Fig. 2*D*). This pattern was found in our case and has also been described in some of the cases of idiopathic hypertrophy of the heart.

SUMMARY

Evidence is presented which suggests that some cases of idiopathic hypertrophy of the heart, described in the older literature, represent end stages of glycogenosis of the heart, and that our first case represents a transition between the infantile, fully developed picture of massive glycogen deposition, and the end stage, with only reactive inflammation, degeneration, and fibrosis.

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THE SIMULTANEOUS ACTION OF CERTAIN DRUGS ON THE BLOOD PRESSURE AND ON THE FLOW IN THE RIGHT AND LEFT CORONARY ARTERIES

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IN A previous paper,[1] the influence of certain drugs on the blood flow in the right and left coronary arteries of the trained dog was reported. Two series of experiments were done; in one, the flow in the right coronary artery was studied, and, in the other, the flow in the left coronary artery. Although the results obtained on the trained dog had clearly indicated a similarity in the response of the flow in the two coronary arteries to these drugs, simultaneous observations on the blood flow in these vessels and a knowledge of the behavior of the arterial blood pressure during the experiments were considered desirable. Such relatively extensive procedures were believed to be excessive for the trained dog. However, it proved feasible to observe simultaneously the action of drugs on the coronary arteries and the blood pressure of the anesthetized dog. The recognized disadvantages of using an anesthetic (chloralosane) were offset by the advantage of being able to obtain more complete information with respect to the action of each of the drugs used. In addition, it would be possible to evaluate the influence of anesthesia on coronary flow by comparing the results of such experiments with the data already obtained on the trained animal. For these and other reasons, experiments were done with the following ten drugs: amyl nitrite, nitroglycerin, theophyllin-ethylenediamine (aminophyllin), histamine acid phosphate, acetyl-β-methylcholine chloride (mecholyl), papaverine, epinephrine, pitressin, pyridine-β-carbonic acid diethylamide (coramine), and atropine sulfate.

METHOD

The thermostromuhr method was used, as in previous experiments reported from this laboratory.[2, 3]

Dogs which weighed from 15 to 38 kg. were used. Under chloralosane anesthesia and artificial respiration, the two units were applied. On the left side, the chest was opened through the fifth intercostal space, and, after incising the pericardium, and after the necessary dissection, a thermostromuhr unit of proper caliber was applied to the circumflex branch of the left coronary artery as near its origin as was practicable. The pericardium and chest were then closed in the usual manner. The right coronary artery was approached in the same manner, through the fourth intercostal space on the right side of the chest, and a thermostromuhr unit was

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TABLE I

THE SIMULTANEOUS EFFECT OF CERTAIN DRUGS ON BLOOD FLOW IN THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY AND THE RIGHT CORONARY ARTERY (CHLORALOSANE ANESTHESIA)

DOG WEIGHT, KG.	DRUG AND DOSE	CONTROL FLOW, C.C. PER MINUTE	MAXIMAL FLOW, C.C. PER MINUTE	PERCENTAGE INCREASE OR DECREASE	COMMENT
35	Amyl nitrite	L 80	115	+44	Returned to control level after 1 min.; followed by a decrease of 21 per cent, lasting more than 7 min.
	inhalation	R 21.5	37	+72	Returned to control level after 1.5 min.; followed by a decrease of 15 per cent, lasting more than 7 min.
38	Nitroglycerin 1.3 mg.	L 180	600	+233	Returned to control level after 4 min.; no subsequent decrease.
		R 83	178	+114	Returned to control level after 2 min.; followed by a decrease of 25 per cent for more than 4 min.
22	Nitroglycerin	L 116	150	+29	Returned to control level after 1 min.; followed by decrease of 14 per cent for 1.5 min.
	1.3 mg.	R 77	122.5	+59	Returned to control level after 1.5 min.; followed by a decrease of 12 per cent for more than 3 min.
35	Nitroglycerin 0.65 mg.	L 67	116	+73	Returned to control level after 2 min.; no significant decrease.
		R 21	37	+76	Returned to control level after 1 min.; followed by a decrease of 29 per cent for 5 min.
35	Aminophyllin 0.24 Gm.	L 85 R 24	310 56	+265 +133	Had not returned to control level after 14 min.
22	Aminophillin 0.24 Gm.	L 120 R 64	182 106	+52 +66	Had not returned to control level after 9 min.
38	Histamine acid phosphate 0.5 mg.	L 145	500	+245	Returned to control level after 3 min.; followed by decrease of 20 per cent for more than 3 min.
		R 59	284	+381	Returned to control level after 2.5 min.; followed by decrease of 37 per cent for more than 3 min.
18.4	Histamine acid phosphate 0.25 mg.	L 126	300	+138	Returned to control level after 5 min. No decrease.
		R 61	258	+323	Had not returned to control level after 11 min. No further decrease.
22	Histamine acid phosphate 0.5 mg.	L 114	170	+49	Returned to control level after 1 min. No significant decrease.
		R 66	130	+97	Returned to control level after 1.5 min. No significant decrease.
15.7	Papaverine 20 mg.	L 40	80	+100	Returned to control level after 7 min. No significant decrease.
		R 23	44	+91	Returned to control level after 2.5 min. No significant decrease.

TABLE I—CONT'D

DOG WEIGHT, KG.	DRUG AND DOSE	CONTROL FLOW, C.C. PER MINUTE	MAXIMAL FLOW, C.C. PER MINUTE	PERCENTAGE INCREASE OR DECREASE	COMMENT
20	Papaverine 20 mg.	L 108	146	+35	Returned to control level after 4 min. No decrease.
		R 20	29	+45	Had not returned to control level after 6 min. No decrease.
35	Epinephrine 0.05 mg.	L 45	113	+151	Had not returned to control level after 9 min. No decrease.
		R 13.5	25	+85	Returned to control level after 3 min. No decrease.
22	Epinephrine 0.05 mg.	L 124	215	+73	Returned to control level after 2 min.
		R 67.5	114	+69	Returned to control level after 2.5 min.
35	Epinephrine 0.05 mg.	L 78	200	+156	Returned to control level after 2 min. No significant decrease.
		R 26	60	+131	Returned to control level after 2 min. No significant decrease.
15	Epinephrine 0.025 mg.	L 70	194	+177	Had not returned to control level after 9 min.
		R 34.5	113.5	+229	Had not returned to control level after 9 min.
22	Pitressin 2 pressor units	L 132	85	-36	Had not returned to control level after 19 min.
		R 76	15	-80	Had not returned to control level after 19 min.
19	Pitressin 0.5 pressor unit	L 63	35	-44	Returned to control level after 9 min.
		R 15	less than 10	-	Had not returned to control level after 14 min.
22	Coramine 250 mg.	L 126	142	+13	Returned to control level after 2 min. No significant decrease.
		R 69	81	+17	
15.7	Atropine sulfate 2 mg.	L 35	47	+34	Still maximally increased 23 min. after the injection.
		R 22	31	+41	

applied to that vessel near its origin. The pericardium and chest were then closed, and normal respiration was restored. In a few instances, however, the chest was left open and artificial respiration was maintained throughout the experiment. The left femoral artery was cannulated, and the mean arterial blood pressure was recorded optically. The right femoral vein was exposed for the injection of drugs, all of which, with the exception of amyl nitrite, were given intravenously.

RESULTS

To conserve space only one reaction to each drug will be described; the essential data on a number of representative experiments are recorded in Table I. Much of the literature which is concerned primarily with the effect on coronary flow of the drugs under consideration was dealt with in our previous paper.[1] For the sake of brevity, many pertinent references have been omitted in this report.

1. *Amyl nitrite.*—A dog which weighed 38 kg., with a mean blood flow of 180 c.c. per minute in the circumflex branch of the left coronary artery and 115 c.c. per minute in the right coronary artery, had a mean

blood pressure of 137 mm. of mercury and a heart rate of 133 beats per minute. The contents of one ampule (0.33 c.c.) of amyl nitrite were given by inhalation through an intratracheal tube for four minutes. Ten seconds after the beginning of the inhalation, the blood flow in both coronary arteries increased; the maximal flow was 511 c.c. per minute in the circumflex branch and 398 c.c. per minute in the right coronary artery. These maximal increases were reached within one minute, and, although the administration of amyl nitrite was continued for four minutes, the blood flow in the circumflex branch had returned to its control level within three minutes, and, in the right coronary artery, within six minutes. The blood pressure decreased to 130 mm. of mercury and returned to its control value after seven minutes. The heart rate, after an increase to 180, returned to the control level after two minutes and thirty seconds. The reactions to amyl nitrite were not always the same as the one described. In some cases the fall in blood pressure was greater and more prolonged; the heart rate sometimes remained increased after the blood flow had returned to its control value. Generally, the blood flow returned rapidly to the control level, but, in one experiment, the increase in flow was followed by a decrease which amounted to 21 per cent and lasted about seven minutes.

2. *Nitroglycerin.*—A dog which weighed 18.4 kg., with a blood flow of 135 c.c. per minute in the circumflex branch and 46 c.c. per minute in the right coronary artery, had a mean blood pressure of 140 mm. of mercury and a heart rate of 114 per minute. Nitroglycerin (1.3 mg. in 1 c.c. of saline solution) was given intravenously in fifteen seconds. Before the end of the injection, the blood pressure began to decrease and soon reached 105 mm. of mercury. At the same time, the blood flow increased in both the circumflex branch and the right coronary artery; the maximal flow was reached in less than one minute in both arteries. The maximal flow in the circumflex branch was 381 c.c., and, in the right coronary artery, 223 c.c. per minute. The heart rate when the blood pressure was lowest was 180 per minute. The blood pressure returned to its control level within fifteen minutes; the heart rate remained at about 180 during this time; the blood flow in both coronary arteries regained its control value about four minutes after the beginning of the injection (Fig. 1).

In all of the experiments the reactions to nitroglycerin were similar; sometimes, however, after the initial increase in flow, there was a decrease below the control value of as much as 29 per cent which continued as long as five minutes.

3. *Theophyllin-ethylenediamine (aminophyllin).*—A dog which weighed 18 kg. had an average flow of 116 c.c. per minute in the circumflex branch and 44 c.c. per minute in the right coronary artery. The blood pressure was 160 mm. of mercury, and the heart rate, 120 per minute. This animal was given 0.48 Gm. of aminophyllin intra-

venously in fifteen seconds. Before the end of the injection the flow increased in both right and left coronary arteries and reached its maximum in both arteries at the same time. The maximal flow was 394 c.c. per minute in the circumflex branch and 258 c.c. per minute in the right coronary artery; then the flow in both arteries decreased progressively, but very slowly. After twenty-eight minutes, the flow in both was still increased. Twenty seconds after the beginning of the injection, the mean systemic arterial pressure dropped to 90 mm. of mercury and then progressively increased, but after twenty-eight minutes it was still below the control level. The heart rate increased to 150 beats per minute.

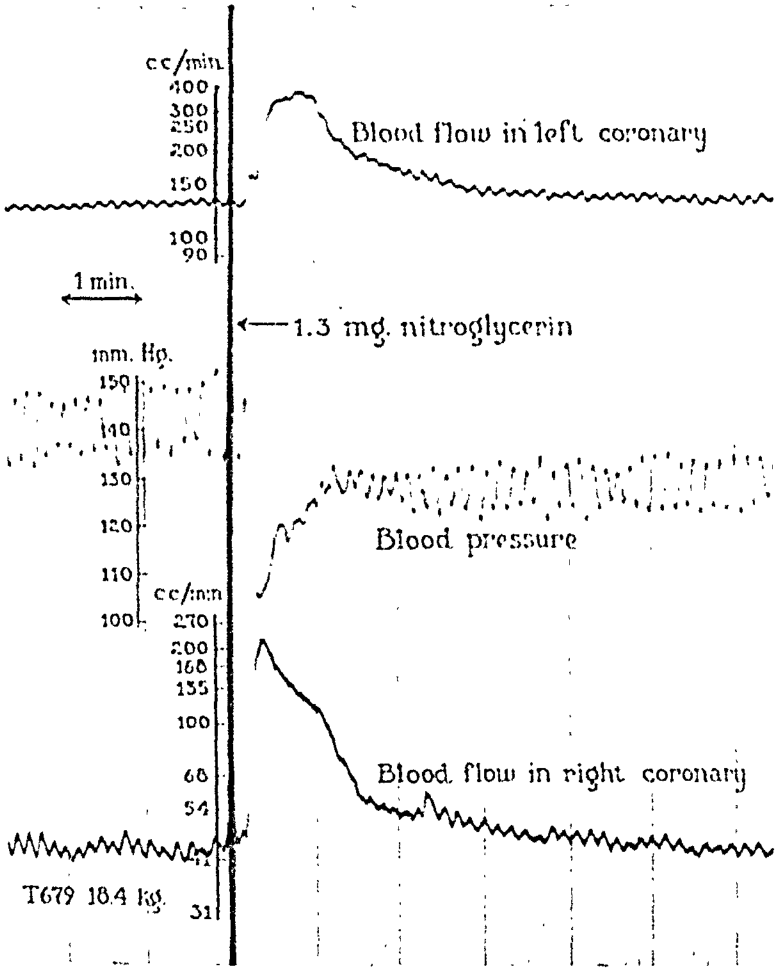

Fig. 1.—The effect of giving 1.3 mg. of nitroglycerin. This and the following figures are simultaneous photographic records of the coronary blood flow, in cubic centimeters per minute, in the circumflex branch of the left coronary artery (upper tracing), the blood pressure, in millimeters of mercury (middle tracing), and the blood flow, in cubic centimeters per minute, in the right coronary artery (lower tracing) of the dog under chloralosane anesthesia. The heavy, vertical line indicates the intravenous administration of the drug in each instance.

In some experiments the blood flow in the coronary arteries was still above the control level after the blood pressure had reached the preinjection level. Regardless of the dose of aminophyllin, there was never a significant decrease below the control level in the coronary

blood flow after the initial increase; this is in contrast to what sometimes occurred with certain of the other drugs.

In all but one experiment, the flow increased more in the right coronary artery than in the circumflex branch. The data which we have do not provide an adequate explanation for this fact.

4. *Histamine acid phosphate.*—A dog which weighed 35 kg., with a mean blood flow of 225 c.c. per minute in the circumflex branch and 68 c.c. per minute in the right coronary artery, had a mean blood pressure of 145 mm. of mercury and a heart rate of 150 beats per minute. An injection of 0.25 mg. of histamine acid phosphate, given in fifteen seconds, caused, simultaneously, a fall in blood pressure and an increased flow in both coronary arteries. The blood pressure dropped to a minimum of 110 mm. of mercury, and the heart rate increased to 180 beats per minute. As was the case with the other agents that caused hypotension, the minimal blood pressure level almost coincided with the maximal blood flow in both coronaries, which was 475 c.c. per minute in the circumflex branch and 155 c.c. per minute in the right coronary artery. The flow in the circumflex branch was back to normal one minute and thirty seconds, and, in the right coronary artery, two minutes and thirty seconds, after the injection. At the time the coronary flow had returned to its control level, the blood pressure was still relatively low, but eventually it returned to its initial level. After the increase, there was a decrease in the blood flow in the circumflex branch to a maximum of 19 per cent below the control level; the decrease lasted seven minutes. In the right coronary artery, the subsequent decrease was not significant (Fig. 2).

This is the typical reaction to such doses of histamine, when given intravenously. Occasionally, however, the blood pressure came back to its control value before the coronary blood flow. It should be stated, also, that sometimes the decrease in coronary flow which follows the initial increase may be very pronounced and of relatively long duration. In one experiment the flow decreased as much as 76 per cent in the circumflex branch and 55 per cent in the right coronary artery, and the flow in both coronary arteries remained decreased for eleven minutes.

5. *Acetyl-β-methylcholine chloride (mecholyl).*—A dog which weighed 35 kg., with a mean flow of 183.5 c.c. per minute in the circumflex branch and 65.5 c.c. per minute in the right coronary artery, and a mean blood pressure of 118 mm. of mercury, was given an injection of 0.5 mg. of mecholyl in fifteen seconds. During and immediately after the injection the flow in both arteries underwent rapid changes; there was first a rapid increase, and then a rapid decrease, but thirty seconds after the beginning of the injection the flow increased. The maximal flow in the circumflex branch was 300 c.c. per minute, and, in the right coronary artery, 101 c.c. per minute. In the right coronary artery the flow had returned to its control level after four minutes, but in the circumflex branch it was still increased thirteen minutes after the injection. The

blood pressure fell to 50 mm. of mercury within one minute after the injection and then rose progressively, but it was still decreased thirteen minutes after the injection. The heart rate increased after the injection.

6. *Papaverine.*—A dog which weighed 15 kg. had a control flow of 45 c.c. per minute in the circumflex branch and 13 c.c. per minute in the right coronary artery. The mean blood pressure was 145 mm. of mercury. At the end of an intravenous injection of 20 mg. of papaverine, given in fifteen seconds, the flow in the circumflex branch and right coronary artery increased to a maximum of 112 c.c. and 30 c.c. per minute, respectively. The blood pressure, which was decreased, did not return to its control level within that time; neither did the heart rate, which was increased. In the experiments with this drug, the increase in coronary flow was not followed by a period when the flow was below the control level (Fig. 3).

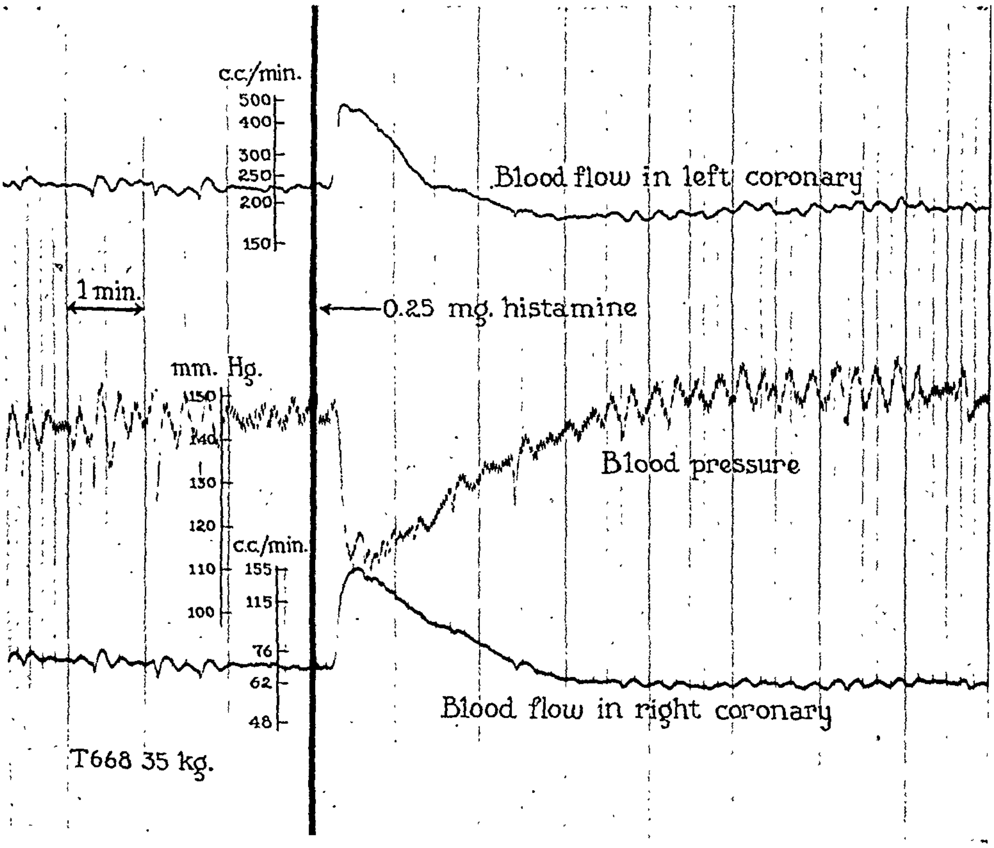

Fig. 2.—The response elicited by 0.25 mg. of histamine acid phosphate.

7. *Epinephrine.*—A dog which weighed 15 kg., with a mean flow of 30 c.c. per minute in the circumflex branch and 11 c.c. per minute in the right coronary artery, a mean blood pressure of 120 mm. of mercury, and a heart rate of 138 per minute, was given 0.025 mg. of epinephrine intravenously in fifteen seconds. Ten seconds after the beginning of

the injection, the blood pressure and the flow in both coronary arteries were simultaneously augmented. The blood pressure increased to 160 mm. of mercury; the blood flow in both coronary arteries became maximal thirty seconds after the beginning of the injection. The flow in the circumflex branch was 110 c.c. per minute, and, in the right coronary artery, 40.5 c.c. per minute. The heart rate decreased to 84 and then increased progressively when the blood pressure and coronary flow started to decrease. The blood pressure, heart rate, and the flow in both coronary arteries returned progressively to their control values in about the same time, from two to three minutes. However, the flow in the circumflex branch then decreased to a maximum of 17 per cent and remained decreased for more than ten minutes, as did the blood pressure. The flow in the right coronary artery did not undergo any significant decrease below the control values.

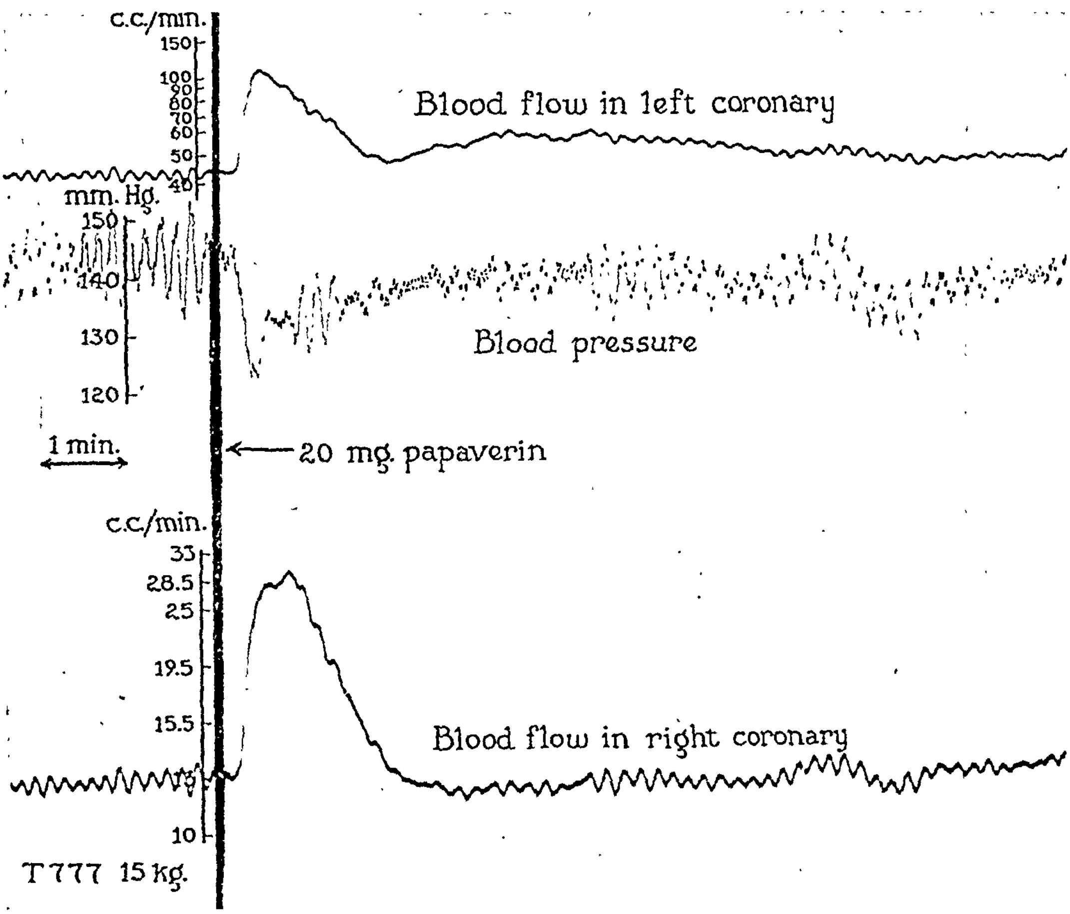

Fig. 3.—The reaction produced by 20 mg. of papaverine.

This reaction to epinephrine is typical; however, the increase in flow and blood pressure may sometimes last somewhat longer. There was not always a period of decreased flow after the initial increase. Sometimes the blood pressure had returned to, or was even below, its control value while the flow in both coronaries was still increased.

8. *Pitressin.*—A dog which weighed 15 kg. had a mean blood flow of 40 c.c. per minute in the circumflex branch and 12 c.c. per minute in

the right coronary artery. The mean blood pressure was 137 mm. of mercury, and the heart rate was 150 per minute. This animal was given 0.5 pressor unit of pitressin in fifteen seconds. The blood flow did not change very much until thirty seconds after the beginning of the injection, when the blood pressure rose to 150 mm. of mercury and the heart rate decreased to 108 beats per minute. Thirty seconds after the beginning of the injection, the blood flow decreased in both coronary arteries. The minimal flow, which was 20 c.c. per minute in the circumflex branch and less than 10 c.c. per minute in the right coronary artery, occurred three minutes after the beginning of the injection. The flow in the circumflex branch gradually returned to its control value in fourteen minutes, but in the right coronary artery the flow remained minimal longer, and, although it rose toward its control value, it was not yet back after eighteen minutes. The blood pressure had resumed its control value about one minute after the beginning of the injection, but the heart rate remained very slow; the minimal rate was 78 beats per minute, or about half the control rate (Fig. 4). Sometimes the blood pressure increased more than in the experiment described; sometimes, after the first increase, the blood pressure fell below the control level. Whatever the state of the blood pressure, the change in the coronary flow induced by pitressin was always a significant and long-lasting decrease.

9. *Pyridine-β-carbonic acid diethylamide (coramine).*—A dog which weighed 22 kg. had a mean blood flow of 130 c.c. per minute in the circumflex branch and 70 c.c. per minute in the right coronary artery. The mean blood pressure was about 128 mm. of mercury. After the injection of 500 mg. of coramine in fifteen seconds, the blood pressure decreased to 115 mm. of mercury and the blood flow in both arteries decreased for a few seconds; then the blood pressure increased to 147 mm. of mercury, and, at the same time, the blood flow increased; the flow reached a maximum of 200 c.c. per minute in the circumflex branch and 98 c.c. per minute in the right coronary artery; the blood pressure returned to normal four minutes after the beginning of the injection, but, even so, the blood flow was still increased in the circumflex branch, in which the flow had not yet resumed its control value eight minutes after the injection. In the right coronary artery the flow was back to normal after two minutes (Fig. 5). This reaction was very much the same as that in all of the other experiments, although in some of them the blood pressure did not increase significantly. The effect of coramine on the blood pressure in these experiments was in striking contrast to its effect in another group of experiments in this laboratory, in which, in dogs under pentothal sodium anesthesia, it always lowered the blood pressure.

10. *Atropine sulfate.*—A dog which weighed 20 kg. had a mean blood flow of 111 c.c. in the circumflex branch of the left coronary artery and 25 c.c. per minute in the right coronary artery. The mean blood pres-

sure was 105 mm. of mercury, and the heart rate 120 per minute. This animal was given 1.5 mg. of atropine sulfate in fifteen seconds. The blood flow in the circumflex branch and right coronary artery increased progressively to a maximum of 133 c.c. and 33 c.c. per minute, respectively. Twenty-three minutes after the injection, the flow was the same. The blood pressure did not change significantly after the injection, but the heart rate increased to 150 beats per minute. The results

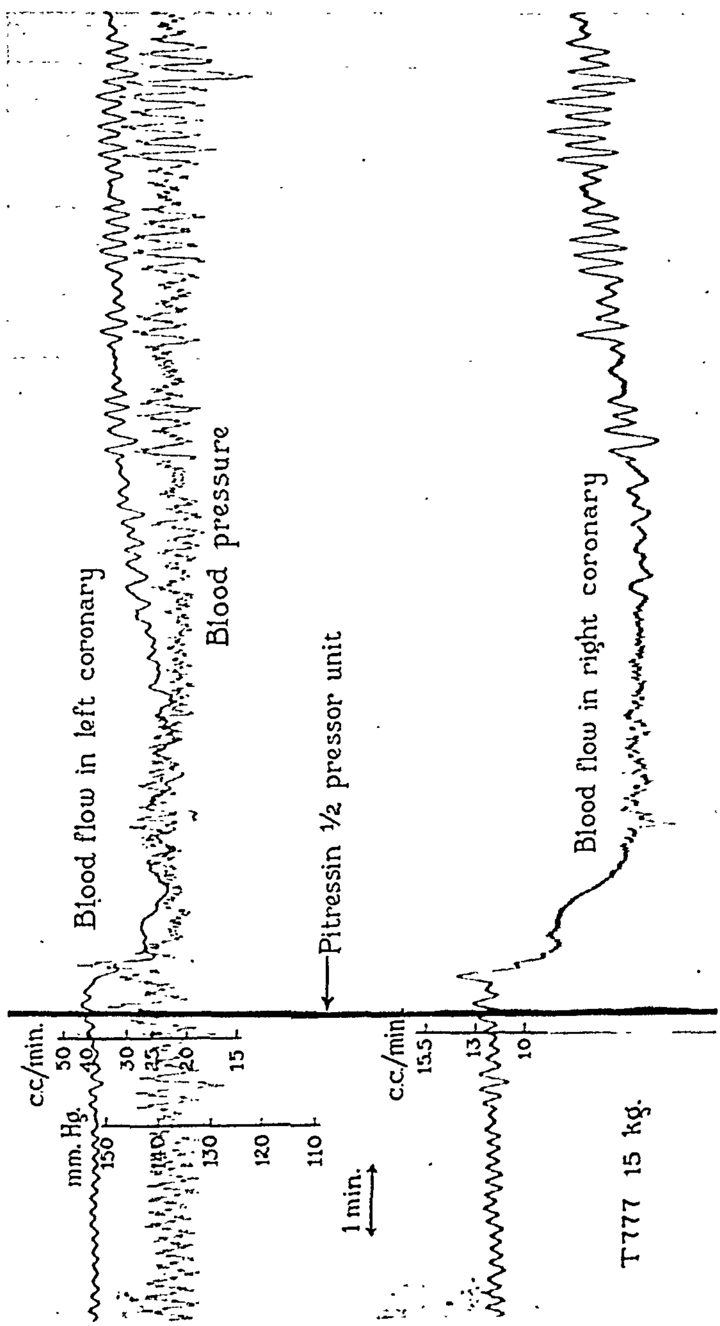

Fig. 4.—The effect of 0.5 pressor unit of pitressin.

in the other experiments with atropine sulfate were similar, except that in certain of them the blood pressure was moderately increased. In some cases the flow reached its maximum within one or two minutes and remained at this level for more than one hour.

COMMENT

The importance of the blood pressure has been emphasized so frequently in connection with the coronary circulation that the role of other factors has been somewhat overshadowed. As the data just presented clearly show, there are, in the intact animal, mechanisms which are capable of increasing the blood supply to the myocardium even when the blood pressure has been greatly lowered by the administration of certain drugs. It may be of interest to consider and attempt to evaluate the possible mechanisms by which these different drugs induce changes in coronary flow.

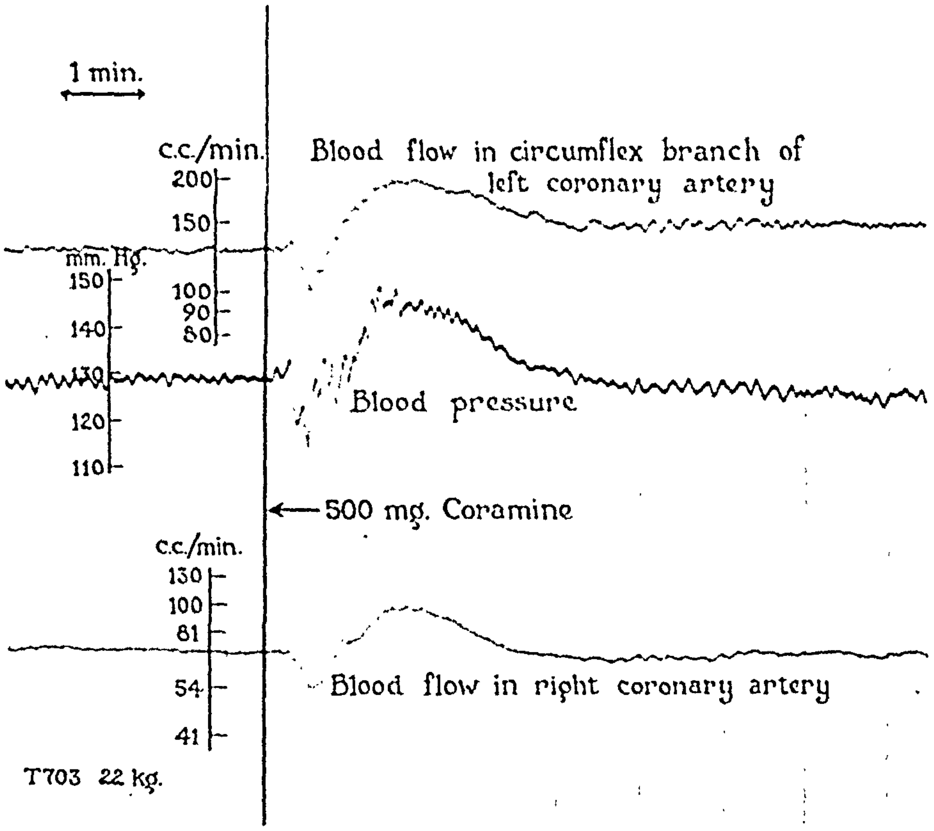

Fig. 5.—The response to 500 mg. of coramine.

Whenever the influence of drugs on the coronary circulation is discussed, the question whether they dilate the coronary vessels is always pertinent. Smith[4] and Voegtlin and Macht[5] concluded from their experiments that the nitrites produce a dilatation of the coronary vessels. Fowler, Hurevitz, and Smith[6] reported that aminophyllin aids in the development of a collateral coronary circulation in the dog, and the result, they concluded, is dependent for the most part on its dilating action on arterioles and capillaries. Anrep[7] reported that histamine dilates the coronary vessels, and he also obtained increases in the coronary flow in the heart-lung preparation and the intact animal with injections of

acetylcholine. Weinstein, Jochim, and Bohning,[8] using acetylcholine and acetyl-β-methylcholine chloride, reported an increase in the coronary perfusion flow in the isolated, fibrillating heart which had been prepared by the method of Katz, Jochim, and Bohning.[9] Under the conditions of their experiments, vasodilatation was considered the sole cause of the increased flow. Anrep[7] found that papaverine increased the coronary flow in a human heart-lung preparation. In our experiments, amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the arterial blood pressure and increased both heart rate and coronary flow.

Whatever may be one's bias with respect to evidence regarding vasodilatation of the coronary vessels, it may be stated with assurance that the augmentation in coronary flow which was observed following the administration of these drugs was caused by a decrease in the effective peripheral resistance in the coronary circulation. That this is true can be demonstrated by the formula: Index of peripheral resistance varies as $\frac{\text{pressure}}{\text{flow}}$. Amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the head of pressure in the coronary arteries by lowering systemic arterial pressure, which, in the absence of other influences, should decrease coronary blood flow,[10] but, since these drugs produced an augmentation of coronary flow, it must follow that the peripheral resistance of the coronary circulation was reduced. Confirmation of this conclusion was obtained from the data on the action of certain drugs by applying, under the following conditions, the formula already given. When the flow in the right and left coronary arteries is known, and when the mean blood pressure in the femoral artery is assumed to correspond to the pressure in the main branches of the coronary arteries, a close approximation of the index of peripheral resistance can be obtained. When the data from a series of observations on the effect of nitroglycerin, aminophyllin, and histamine acid phosphate were dealt with in this way, the effective peripheral resistance was found to be decidedly decreased in both coronary arteries, as shown in Table II. We are not prepared to state in exactly what way the effective peripheral resistance was reduced by all of the drugs used. The possibility that the drugs may act directly on the musculature of the coronary vessels should be considered. Since the nitrites are known to dilate the systemic blood vessels, it is very probable that they also dilate the coronary blood vessels. The dilating effect of the other drugs may be, at least in part, the result of a direct action. It is conceivable that certain drugs may act on the coronary vessels by affecting the peripheral endings of the cardiac nerves.

The possibility that certain vasomotor reflexes may influence the coronary circulation should be mentioned. Since it has been shown by Stella[11] (whose observations we have confirmed[12]) that a fall of pressure in the carotid sinus causes an increase, and a rise of pressure causes

TABLE II

CHANGES IN THE INDEX OF PERIPHERAL RESISTANCE PRODUCED BY CERTAIN DRUGS

DOG, WEIGHT	DRUG	DOSE (MG.)	INDEX OF PERIPHERAL RESISTANCE					
			RIGHT CORONARY ARTERY			LEFT CORONARY ARTERY		
			BEFORE INJECTION	AFTER INJECTION	PER CENT REDUCED	BEFORE INJECTION	AFTER INJECTION	PER CENT REDUCED
20 kg.	Epinephrine	0.25	8.02	2.59	67.7	2.04	0.61	70.1
	Nitroglycerin	1.3	6.42	1.62	74.8	1.56	0.58	62.8
1	Histamine	0.25	5.95	1.95	67.2	1.32	0.40	69.7
	Aminophyllin	240	5.31	3.11	41.4	1.29	0.82	36.4
	Epinephrine	0.10	8.33	3.22	61.3	1.67	0.54	67.7
35 kg.	Histamine	0.25	2.07	0.74	64.2	0.64	0.24	62.5
	Epinephrine	0.10	2.35	0.91	61.3	0.89	0.27	69.7
2	Nitroglycerin	1.3	2.51	1.11	55.8	0.95	0.63	33.7
	Nitroglycerin	1.3	2.07	1.06	48.8	0.86	0.62	27.9
	Aminophyllin	480	2.18	0.91	58.2	0.83	0.45	45.8

a decrease, in coronary flow, all of the drugs which we used may conceivably owe part of their influence on the coronary flow to this factor. It is also probable that the doses of the drugs used in our experiments caused an increase in cardiac output.[13, 14] This possibility must be considered, for increased cardiac output, alone, has been shown by Anrep and Segall[15] to augment the coronary flow in the innervated heart-lung preparation.

Markwalder and Starling[16] have stated that epinephrine dilates the coronary vessels. Morawitz and Zahn[17] found that the coronary blood flow was increased after the injection of epinephrine into the intact animal; Anrep,[7] confirming Rein's experiments, reported that small doses of epinephrine produced a very slight increase, and sometimes a decrease, of the coronary flow in the presence of the vagi, but the same doses in the absence of the vagi, or larger doses even in the presence of the vagi, always produced a large increase in coronary flow. In our experiments, epinephrine increased both blood pressure and coronary flow; at the same time the heart rate changed continuously.

Since the head of pressure in the coronary vessels is increased by epinephrine, it is of importance to attempt to ascertain whether the increased flow is brought about by this factor alone, or partly by this and partly by a decrease in the effective peripheral resistance. The changes in the index of peripheral resistance were ascertained by means of the formula already stated. In a series of observations, the index of peripheral resistance was shown to be greatly reduced (Table II). It is evident that the effective peripheral resistance of the coronary circulation is decreased; this, in the presence of a greatly increased blood pressure, should and does result in a much augmented coronary flow. Another factor to be considered is the possibility that epinephrine acts directly on the coronary vessels. As we have already stated, the rise in blood pressure, alone, increases coronary flow, but, through its effect on the carotid sinus mechanism, it should tend to decrease coronary

flow. The influence of changes in cardiac output may likewise have a bearing on the results with epinephrine. Whatever the various possible mechanisms are, the end result is an increased flow of blood through the coronary arteries.

With coramine, an increase in both coronary flow and blood pressure occurred. Judging from the work of Greene[18] and of Stoland and Ginsberg,[19] and from previous observations in this laboratory, we expected a fall in blood pressure. For the most part the statements made with regard to epinephrine apply as well to a consideration of the mechanism of the action of coramine, except that a significant increase in coronary flow was sometimes observed in the absence of a significant increase in the blood pressure. This would tend to show that the increase in coronary flow produced by coramine may be the result, at least in part, of a decrease in the effective peripheral resistance.

Anrep and Stacey,[20] Gruber and Kountz,[21] Melville,[22] and others have shown that pitressin decreases the coronary flow by producing a constriction of the coronary vessels. In our experiments, pitressin always produced a startling decrease in the coronary flow. The pressure increased, but sometimes it fell after a few minutes, even below the control level; usually, however, the initial increase was maintained for a few minutes before the return to the control level occurred. The heart rate was always decreased. The increase in blood pressure, alone, tends to increase the coronary flow, whereas the reflexes induced by the increase tend to decrease the coronary flow.[11, 12] Regardless of the blood pressure, however, the coronary flow was always decreased. The possibility that changes in cardiac output produced by pitressin might affect the coronary flow should not be overlooked.

Calculations of the index of peripheral resistance indicate that the reduction in coronary flow following injections of pitressin is caused by a marked increase in the peripheral resistance of the coronary circulation, which, it seems reasonable to assume, results from vasoconstriction of the coronary vessels. However, we cannot rule out the possible influence of changes in the tonus of the extravascular support except on the basis of the work of Anrep and Stacey,[20] who concluded, from a study of the effects on the heart of epinephrine, carbon dioxide, pituitary extract, and caffeine, that the influence of these substances on the strength of cardiac contraction, as measured by changes in heart volume, bore no relation to their effect on coronary blood flow.

Wiggers[23] and Anrep and Segall[15] have shown that atropine increases the coronary flow. In our experiments, atropine sulfate increased both coronary flow and heart rate. The changes in blood pressure were not great; the blood pressure increased very slightly or often not at all, so that we can say that the increase in coronary flow was caused almost exclusively by a decrease in the effective peripheral resistance of the coronary circulation.

SUMMARY AND CONCLUSIONS

Under chloralosane anesthesia, simultaneous studies were made on the effect of certain drugs on the blood flow in the right coronary artery and the circumflex branch of the left coronary artery, as well as on the mean, femoral, arterial blood pressure.

In general, the coronary flow in both the right coronary artery and the circumflex branch of the left coronary artery was greater than in trained dogs of the same size.

The blood flow in the circumflex branch of the left coronary artery was, on the average, 2.66 times that in the right coronary artery.

Changes in flow induced by the drugs which we studied were qualitatively the same in the right coronary artery and the circumflex branch.

Amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the mean blood pressure and, as in the trained animal, increased both heart rate and coronary flow. The increase of coronary flow is caused by a diminution of the effective peripheral resistance in the coronary circulation.

Epinephrine increased both blood pressure and coronary flow; the increase in coronary flow was produced by an increased head of pressure and by a decrease in effective peripheral resistance.

Pitressin increased blood pressure and decreased heart rate and coronary flow; the decrease of coronary flow appears to be caused by an increase of the effective peripheral resistance in the coronary vessels.

Pyridine-β-carbonic acid diethylamide (coramine), under the conditions of our experiments, increased blood pressure and coronary flow, but the increase of coronary flow was the result, at least in part, of a decrease in the effective peripheral resistance of the coronary circulation.

Atropine sulfate increased heart rate and coronary flow, but it affected blood pressure very little; the increase in coronary flow was caused almost exclusively by a decrease in the effective peripheral resistance of the coronary circulation.

Whether the decrease in effective peripheral resistance which was produced by the various drugs was effected by active relaxation of the intrinsic musculature of the coronary vessels or by changes in the tonus of the extravascular support, or both, was not ascertained.

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STUDIES ON THE AURICULOVENTRICULAR CONDUCTION TIME OF NORMAL CHILDREN AND OF RHEUMATIC CHILDREN WITHOUT SIGNS OF RHEUMATIC ACTIVITY

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IN USING any laboratory test as an aid in the diagnosis of disease, it is essential to know the range of variations in normal persons. Most observers agree that, in adults, an auriculoventricular conduction time of more than 0.20 second is abnormal.[1, 2, 3] It is generally accepted that the A-V conduction time of children is shorter than that of adults. According to some authors,[3] the upper normal limit for children less than 18 years of age, with heart rates of 71 to 90 beats per minute, is 0.18 second. Another observer[4] states that the P-R interval in children less than 14 years of age should not exceed 0.16 second.

It is also generally accepted that, with comparable rates, normal persons do not show fluctuations of more than 0.02 second in the P-R interval in tracings taken at different times.[1, 5]

In studying a series of routine electrocardiograms which were taken at intervals of approximately three months on 140 rheumatic children without signs of rheumatic activity, it was noted that the conduction time was more than 0.19 second in eight children without demonstrable evidence of organic heart disease. It was also found that the P-R interval in seven cases in which there were no clinical or laboratory signs of an active rheumatic infection varied 0.04 second, or more, with comparable rates, in tracings taken at different times.

The following questions therefore arose: (1) Can a prolonged P-R interval, in the absence of other signs, be considered an indication of myocardial involvement? (2) Do fluctuations of 0.04 second, or more, in the P-R interval occur in rheumatic children in the absence of an active rheumatic infection?

Incidence of prolonged P-R intervals in rheumatic children without signs of rheumatic activity and with no evidence of organic heart disease.—The electrocardiograms of 140 convalescent rheumatic children who were classified as potential and possible cases of rheumatic heart disease, according to the criteria of the New York Heart Association,[4] were selected for study. The children ranged in age from 7 to 15 years and had been under close observation for long periods of time, varying from six months to two years. The temperature and pulse rate were taken three times daily, and hemoglobin estimations, leucocyte counts, and sedimentation rates were obtained at frequent intervals.

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Teleoroentgenograms and fluoroscopic examinations were made on admission and every six months thereafter. Electrocardiograms were taken every three months, or oftener. None of the children included in the study exhibited any clinical or laboratory signs of rheumatic activity during the period of observation.

The P-R interval in the majority of these children, namely, 132, was 0.18 second, or less. However, eight children (five girls and three boys), or 5.7 per cent of the group, had a conduction time of 0.20 second, or more, in the majority of the tracings. The rheumatic history, period of observation, and number of tracings taken on each of these eight children are summarized in Table I.

Since these eight children had had rheumatic fever, it was possible that the prolonged conduction time might have been the result of scarring of the conducting system. It seemed remarkable, however, that the cardiac involvement in these cases was confined entirely to the conducting system, and that no signs of organic heart disease had developed. A review of the literature showed that prolonged conduction times had occasionally been reported in apparently normal adults and children. It was thought worth while, therefore, to compare the incidence of P-R intervals of 0.19 second, or more, in our rheumatic group with that in 150 normal girls.

The length of the P-R interval in normal persons.—Although a P-R interval of 0.20 second, or more, for adults and of 0.17 to 0.18 second for children is considered abnormal by most observers, it is noteworthy that some of the control series of electrocardiograms of normal subjects published by various authors include a few exceptions. The Lewis and Gilder[1] series of fifty-two medical students included two men with conduction times of 0.20 and 0.21 second, respectively. Among 1809 midshipmen, Ferguson and O'Connell[6] found twenty-six men, or 1.5 per cent, who had conduction times of 0.21 second, or more.

A P-R interval of 0.18 second was reported by Seham[7] in an infant of 11 months, and by Burnett and Taylor[8] in an infant of 18 months. The Lincoln and Nicolson series[9] of 226 normal school children included a healthy boy of 7 years with a conduction time of 0.19 second. Alstead[10] twice found a P-R interval of 0.20 second in a group of 100 normal children whose average age was 12 years.

In addition to these instances of prolonged conduction time in normal adults and children, four cases of normal persons with markedly prolonged P-R intervals have been reported by different observers.[11]

The A-V conduction time of 150 normal girls whose ages ranged from 6 to 16 years.—Electrocardiograms were taken on 150 normal girls.* The P-R interval in the majority of these children, namely, 142, was 0.18 second, or less. Eight girls, however, or 5 per cent, had a P-R interval of 0.19 second, or more; the maximum was 0.24 second. As far as could be ascertained, none of these girls had a history of rheu-

*These children were examined through the cooperation of Dr. Luke Fleming and the Sisters of Mercy, Tarrytown, New York.

TABLE I

RHEUMATIC HISTORY AND PERIOD OF OBSERVATION OF EIGHT RHEUMATIC CHILDREN WITH PROLONGED CONDUCTION TIMES AND NO EVIDENCE OF ORGANIC HEART DISEASE OR RHEUMATIC ACTIVITY*

CASE NO.	NAME	DATE OF BIRTH	SEX	RHEUMATIC ATTACKS AND AGE AT EACH	LENGTH OF STAY AT IRVINGTON HOUSE	ELECTROCARDIOGRAMS NO. OF TRACINGS	DATE	RATE	P-R (SECONDS)
1	P. McG. 3325	9/ 6/27	F	8½ P† and C, March, April, 1936 9½ Rh. fever, May, 1937	6/29/37 to 2/ 1/40	19	6/29/37 8/ 1/38 10/ 9/39	110 110 100	0.20 0.20 0.20
2	E. O'S. 3400	3/12/27	F	4 P, April to June, 1931 8 P and C, July to Aug. 1935 10 Jt. P. and epistaxis, Feb., 1937	6/14/38 to 1/28/39	10	6/14/38 10/21/38 1/27/39	90 90 90	0.22 0.22 0.21
3	C. B. 3357	12/25/23	F	11 P, Ch, and C, March, April, 1935 11½ P and Ch, fall, 1935	9/ 4/37 to 7/25/39	36	9/ 6/37 8/ 3/38 3/ 7/39	80 90 80	0.20 0.20 0.21
4	V. C. 3396	7/ 7/29	F	7 P, May, 1936 8 P, May, 1937	6/14/38 to 2/ 1/40	15	6/14/38 2/ 2/39 8/ 6/39	80 80 90	0.20 0.22 0.21
5	D. McK. 3364	5/31/29	F	7 Ch, May, 1936	9/10/37 to 11/ 1/38	14	12/17/37 10/24/38 10/31/38	80 80 80	0.20 0.20 0.20
6	H. P. 3350	5/31/39	M	6 P and C, Oct., Nov., 1935 8 C, March to May, 1937	8/24/37 to 10/11/39	29	8/25/37 5/13/38 10/ 6/39	80 80 82	0.20 0.20 0.21
7	L. S. 3500	2/16/31	M	6 P-R interval 0.20 seconds in routine physical exam. March, 1937 8 Sore throat, fever, Jt. P., ESR normal, Jan., 1939	7/11/39 to 2/ 1/40	11	7/12/39 7/17/39 9/11/39	80 88 80	0.24 0.24 0.24
8	H. V. 3055	8/23/24	M	8 P, Nov., Dec., 1932 10½ P, Jan. to March, 1935	4/25/35 to 10/17/35 1/ 6/36 to 8/ 4/36	18	9/ 7/35 2/21/36 7/20/36	80 80 80	0.38 0.38 0.20

*With the exception of Case No. 7, no tracings were taken on these children before the onset of rheumatic symptoms.

†The following abbreviations are used in Tables I and III:

P Polyarthritis
C Carditis
Rh. Rheumatic
Jt. P. Joint Pains
Ch Chorea
ESR Erythrocyte Sedimentation Rate

matic fever or chorea. They had lived in the orphanage for periods varying from one to nine years. No rheumatic manifestations had been observed during the course of their stay. On physical and fluoroscopic examination their hearts were found to be normal. Thus, no evidence of a previous rheumatic infection was obtained in any of these children. The heart rates and P-R intervals of these eight girls are presented in Table II.

TABLE II

DATA ON NORMAL GIRLS WITH P-R INTERVALS OF 0.19 SECOND, OR MORE

CASE NO.	NAME	AGE	ELECTROCARDIOGRAM		
			DATE	RATE	P-R (SECONDS)
1	E. S.	11	6/23/39 9/19/39	82 92	0.19 0.19
2	C. U.	14	6/26/39 7/10/39	74 106	0.19 0.19
3	A. M.	15	6/23/39 9/ 4/39	80 90	0.19 0.19
4	M. L.	11	6/24/39 9/14/39	78 100	0.19 0.19
5	J. L.	14	6/16/39 7/10/39	88 88	0.20 0.21
6	E. K.	7	6/20/39 7/19/39 9/13/39	104 100 120	0.21 0.20 0.20
7	R. R.	13	6/26/39 7/18/39 9/12/39	78 88 90	0.20 0.20 0.20
8	M. M.	12	6/26/39 7/10/39 9/12/39	74 82 80	0.24 0.20 0.20

Fluctuations of 0.04 second, or more, in the P-R interval in rheumatic children with no evidence of active rheumatic infection.—Routine electrocardiograms which were taken, when the heart rates were comparable, over periods of six to twenty-four months on the eight rheumatic children with prolonged conduction times showed significant spontaneous variations in three instances. In two cases, the changes amounted to 0.04 or 0.05 second. In the other case, the variations were much more striking; the P-R interval varied from 0.17 to 0.40 second without significant changes in heart rate. This patient (Case 8, Table I), a boy of 11 years, was under close observation for a period of one year and showed no clinical or laboratory signs of rheumatic activity. During this time, eighteen tracings were taken at intervals of approximately three weeks. The P-R interval was greatly prolonged in ten of these tracings, ranging from 0.36 to 0.40 second; in the other eight, it was 0.17 to 0.19 second. This patient has now been followed for a period of four years. During this time he has had no signs of rheumatic activity and has not developed organic heart disease. The tendency to marked fluctuations in the P-R interval was still present when this boy was re-examined at the age of 15 years.

Spontaneous variations in the P-R interval were also noted in four children whose conduction time was 0.15 to 0.16 second in the majority of tracings. None of these children had any demonstrable clinical or laboratory evidence of rheumatic activity during the period of observation.

The spontaneous variations in the P-R interval are summarized in Table III.

Since there was no evidence that these fluctuations in the conduction time were related to an active rheumatic infection in any of these children, it seemed of interest to ascertain whether the degree of variation which we observed exceeded that which occurs in normal persons.

Lewis and Gilder[1] took repeated tracings on twenty-four medical students. In most instances, the P-R interval tended to remain constant. In one case, however, when the heart rates were comparable, a variation of 0.03 second was noted. Cohn and Swift[5] took daily tracings on six normal adults. Although these authors state that, judging from their experience, variations in the conduction time of normal persons are usually less than 0.02 second, in one of their six normal subjects there was a variation of 0.06 second.

Three observers[11a, b, c] have reported marked variations in the P-R intervals of three normal adults. The conduction time of two of these subjects varied 0.12 second (from 0.20 to 0.32 second and 0.22 to 0.34 second, respectively). The variation in the third was 0.17 second (from 0.18 to 0.35 second).

Fluctuations of 0.04 and 0.05 second in the P-R interval in normal children.—In our control series, two or three tracings were taken on the eight girls with a prolonged conduction time. Spontaneous variations of 0.04 to 0.05 second were observed in two instances.

The incidence (5.7 per cent) of prolonged conduction time in the group of 140 rheumatic children with no signs of rheumatic activity and no evidence of organic heart disease was almost the same as that in the control group of 150 normal girls (5 per cent). Since no evidence of a previous rheumatic infection could be obtained in the case of the eight normal children, it was thought that the prolongation of the P-R interval might, in certain instances, be the result of increased vagal tone.

Previous observers who have reported prolonged conduction times in normal subjects have attempted to show that the prolongation was caused by increased vagal activity, rather than by an organic lesion of the conducting system. Ferguson and O'Connell[6] succeeded in reducing the conduction time in two of their cases by the injection of atropine. Other workers[11a, b, c, d] were able to shorten the P-R interval by exercise, as well as by the injection of atropine. Levy[11d] showed that stimulation of the vagus by holding the breath or by pressure on the carotid sinus increased the degree of heart block. Following the administration of atropine, however, holding the breath and carotid sinus pressure were without effect.

TABLE III

SPONTANEOUS VARIATIONS IN THE P-R INTERVAL IN SEVEN RHEUMATIC CHILDREN WITH NO SIGNS OF RHEUMATIC ACTIVITY

CASE NO.	NAME	DATE OF BIRTH	SEX	RHEUMATIC ATTACKS AND AGE AT EACH	LENGTH OF STAY AT IRVINGTON HOUSE	ELECTROCARDIOGRAM		
						DATE	RATE	P-R (SECONDS)
1	E. O'S. 3400	3/12/27	F	See Case 2, Table I	6/14/38 to 1/28/39	6/14/38	90	0.22
						10/20/38	90	0.19
						10/21/38	90	0.22
						10/22/38	95	0.17
						1/27/39	90	0.21
2	C. B. 3357	12/25/23	F	See Case 3, Table I	9/ 4/37 to 7/25/39	9/ 6/37	80	0.20
						6/ 2/38	90	0.18
						1/ 4/39	75	0.22
						2/ 3/39	96	0.21
						3/ 7/39		
						9 A.M.	94	0.17
						noon	90	0.20
						3 P.M.	90	0.21
						5 P.M.	80	0.21
3	H. V. 3055	8/23/24	M	See Case 8, Table I	4/25/35 to 10/17/35 1/ 6/36 to 8/ 4/36	4/26/35	60	0.17
						9/ 7/35	80	0.38
						9/30/35	70	0.40
						10/ 2/35	80	0.36
						10/ 3/35	80	0.39
						10/ 7/35	70	0.17
						10/14/35	80	0.36
						1/ 7/36	70	0.17
						1/24/36	90	0.33
						2/ 7/36	100	0.18
						2/21/36	80	0.38
						3/ 2/36	70	0.40
						3/19/36	110	0.18
						4/ 7/36	80	0.38
						4/23/36	80	0.39
						5/22/36	80	0.16
						6/25/36	80	0.19
						7/20/36	80	0.20
						4/12/39	80	0.19
4	H. O. 3184	7/18/26	M	6 P, March, April, 1932 6 P, May to July, 1932	6/29/36 to 10/11/38	11/ 3/36	84	0.16
						4/13/37	82	0.21
						4/20/37	88	0.17
						5/20/37	90	0.16
						8/ 5/37	90	0.16
						2/14/38	86	0.20
						6/ 6/38	90	0.18
5	B. S. 3430	7/ 3/28	M	9 P, Aug. Sept., 1937	8/ 9/38 to 9/ 5/39	8/10/38	100	0.16
						6/ 8/39	96	0.20
						6/29/39	110	0.16
						7/19/39	110	0.18
						9/ 5/39	108	0.16
6	A. M. 3182	7/25/27	M	Unknown, Rh. family history	5/29/36 to 7/13/37	5/29/36	90	0.15
						11/ 5/36	90	0.20
						11/23/36	90	0.16
						4/27/37	70	0.16
						10/25/39	68	0.16
7	O. G. 3345	1/31/27	F	6 P, May, 1933 10 P, June, 1937	8/10/37 to 2/ 1/40	8/11/37	90	0.16
						1/22/38	108	0.18
						5/29/39	80	0.14
						10/ 2/39	84	0.17

Unfortunately, permission to study the effect of atropine on the eight normal girls with a prolonged auriculoventricular conduction time could not be obtained. Simpler methods of stimulating and inhibiting the vagus were therefore tried, both on the eight normal children and on the rheumatic children whose only abnormality was a prolonged conduction time.

Inhibition of the vagus by exercise.—The children were asked to hop, and tracings were taken when the heart rate had increased 30 to 60 beats a minute.

The P-R interval of one of the girls in the control group was decreased by 0.04 second. The conduction time in the other seven girls remained constant, or was decreased by 0.02 second, or less.

In the rheumatic group, exercise sufficient to increase the rate 30 beats per minute decreased the P-R interval from 0.20 to 0.16 second in one instance. In four other rheumatic children, although the exercise was insufficient to increase the rate significantly, changes were produced. In three, a decrease in the P-R interval of 0.04 second, or more, occurred. In the fourth child, on the contrary, there was an increase in the conduction time from 0.19 to 0.36 second (Case 8, Table I).

Holding the breath in inspiration.—Vagal activity is known to vary with the phases of respiration. In most persons, inspiration increases, and expiration decreases, the action of the vagus. Occasionally, however, the effects of inspiration and expiration are reversed.

The children were asked to take a deep breath and hold it while the tracing was being taken.

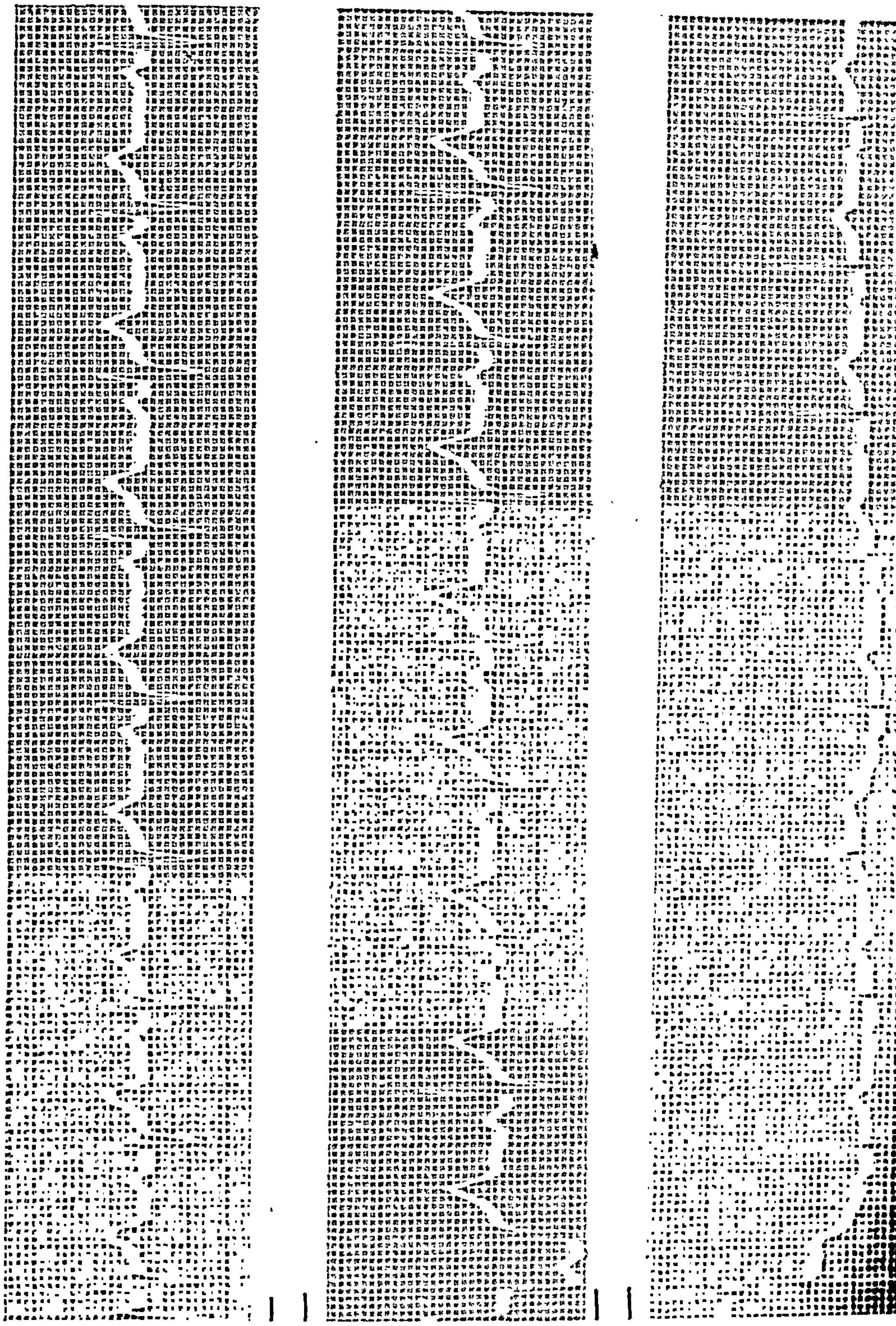
In two *normal* girls, this procedure reduced the P-R interval from 0.20 second during inspiration to 0.16 second during expiration. In another girl, although no significant change in the conduction time occurred, there was a displacement of the pacemaker from the sinoauricular to the auriculoventricular node during expiration. Nodal premature contractions were observed at the height of inspiration in one instance. The girl whose P-R interval varied spontaneously showed a marked response to holding the breath; during expiration the conduction time in certain parts of the record, instead of decreasing, increased 0.06 second. Nodal rhythm was also present occasionally during expiration.

In the *rheumatic* group with prolonged conduction time and no signs of organic heart disease, holding the breath produced no changes.

The effect of exercise and holding the breath in inspiration on six rheumatic children whose conduction times were consistently 0.17 second, or less, was studied. No significant changes were produced.

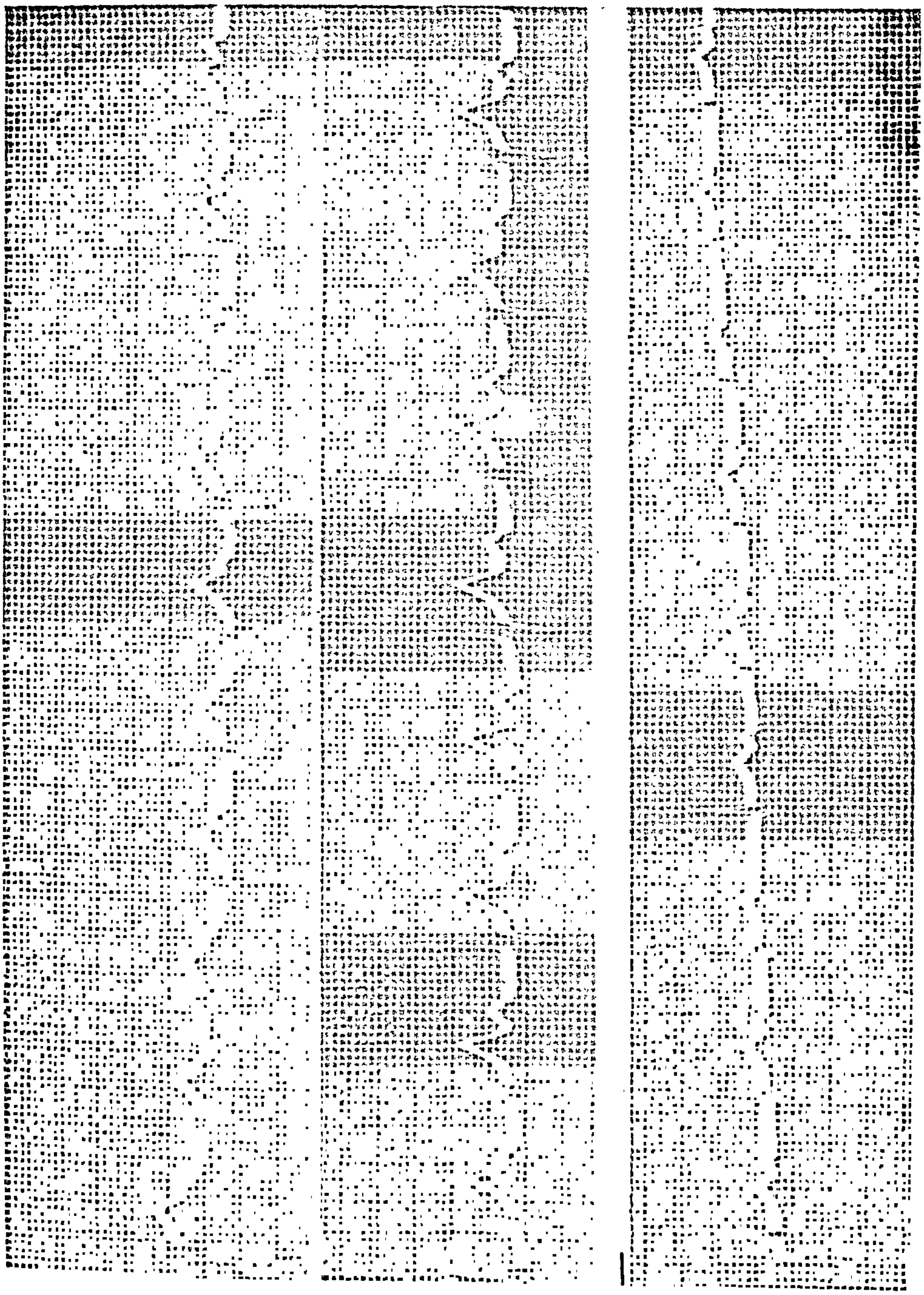
The effect of exercise and holding the breath was also studied on three children with *inactive rheumatic* heart disease who had cardiac enlargement and physical signs of organic valvular disease, associated with a prolonged conduction time. No effect was produced.

Atropine.—The effect of atropine was tried on one boy, 8 years of age, who came of a rheumatic family, but had had no clear-cut rheu-



A.

FIG. 1.—Case 8, Table I. A (April 12, 1939), Routine electrocardiogram. P-R 0.19 sec. B, electrocardiogram taken 10 minutes later, after bending forward 20 times. P-R 0.36 sec.



B.

matic symptoms. His P-R interval was first found to be prolonged during the course of a routine physical examination at the age of 6 years and has been consistently prolonged since that time.

The intravenous injection of 1.0 mg. of atropine produced an increase in rate from 80 to 160 beats per minute, with a reduction of the conduction time from 0.24 to 0.17 second. Thirty minutes after the injection the rate dropped to 120 beats per minute, and the conduction time increased to 0.20 second. The P-R interval in the control tracing, when the rate was 80 beats per minute, was 0.24 second. The importance of the role of the vagus in this case was demonstrated in the following way: Complete heart block was easily induced by pressure on the eyeballs; following the administration of atropine, eyeball pressure had no effect.

In two children with inactive rheumatic heart disease, cardiac enlargement, and physical signs of organic valvular disease, associated with a prolonged conduction time, the intravenous injection of 1.0 mg. of atropine decreased the P-R interval 0.04 second.

In the early stages of acute rheumatic fever, in cases in which the conduction time was prolonged, Bruenn[12] and Keith[13] found that atropine shortened the P-R interval considerably. This suggests that the prolongation of the conduction time which occurs so frequently during the course of an acute rheumatic attack may be caused by an action on the vagus of toxins which are produced during the course of the infection. In our two patients with early organic heart disease and no signs of rheumatic activity, the reduction in the P-R interval was much less striking (0.04 second) than that observed in the active stage of the disease by Bruenn and Keith.

DISCUSSION

The majority of observers agree that the A-V conduction time of children is usually shorter than that of adults and tends to increase with age. Unfortunately, no study of a series of electrocardiograms taken on the same child at yearly intervals has been reported. It is, therefore, not known how much the conduction time of any given person tends to increase with age, or whether an increase of more than 0.02 second (which might be caused by the difference between the heart rates of young children and adults) actually occurs in every case.

In the opinion of most observers, P-R intervals of 0.19 second, or more, in children less than 16 years of age, are considered abnormal. It is of interest, however, that three observers[9, 10] have reported the occurrence of conduction times of 0.19 and 0.20 second in normal children.

In our series of 150 *normal* girls, whose ages ranged from 6 to 16 years, eight, or 5 per cent, had a P-R interval of 0.19 second, or more, with a maximum of 0.24 second. None had a history of rheumatic fever or chorea, and no evidence of rheumatic heart disease was found.

Prolongation of the conduction time in a child with a rheumatic history but no demonstrable heart disease, whose infection is apparently

quiescent at the time of the examination, is usually interpreted as a definite indication that cardiac involvement has occurred. P-R intervals of more than 0.18 second have been reported so rarely in normal children that the accidental discovery of prolongation of the conduction time in the course of a routine physical examination suggests that there may have been a previous, unrecognized rheumatic infection. This is not necessarily the case, however, for prolongation of the conduction time does occur in normal young adults and in normal children. It was thought of interest to consider what factors, other than a rheumatic infection, might cause prolongation of the P-R interval in children.

It is well known that a disturbance in conduction may occur during the course of diphtheria and, occasionally, during pneumonia, influenza, and typhoid fever. In all of these infections, however, the prolongation of the P-R interval usually disappears as the patient recovers.

The occurrence of P-R intervals of 0.20 second, or more, in normal individuals has been explained in various ways. Meyer[11a] thought that it might indicate a congenital abnormality of the His bundle. Reid[11b] was of the opinion that it might be caused by either a congenital malformation of the bundle of His or abnormal activity of the vagus. Ferguson and O'Connell,[6] Marzahn,[11c] and Levy[11d] considered that the prolonged conduction times which they observed were probably the result of increased vagal tone. These authors found that atropine markedly reduced the length of the P-R interval in their cases. On the other hand, it has been shown by Bruenn[12] and Keith[13] that, in normal subjects with short P-R intervals (0.17 second, or less), atropine does not reduce the conduction time significantly. These observations suggest that only when the prolongation of the P-R interval is related to unusual activity of the vagus does atropine reduce the conduction time.

Unfortunately, the use of atropine in our control group of children with prolonged conduction times was not feasible. The effect of simpler methods of stimulating and inhibiting vagal activity, such as exercise and holding the breath, was therefore studied. The results were compared with those which were obtained in a group of rheumatic children who had prolonged P-R intervals but no demonstrable organic heart disease or signs of rheumatic activity. It was found that spontaneous variations of 0.04 second, or more, occurred in both groups. Exercise reduced the conduction time significantly in two of the normal and four of the rheumatic children. In three of the rheumatic children, although the exercise was not sufficient to produce a marked increase in heart rate, it apparently stimulated the sympathetic system, for the P-R intervals were reduced from 0.06 to 0.04 second. In another rheumatic boy, exercise (bending forward 20 times while sitting in a chair) seemed to produce a feeling of apprehension, and the conduction time, instead of being decreased, was increased by 0.17 second.

Other phenomena which are thought to be the result of vagal activity, namely, shortening of the P-R interval during expiration, shifting of the pacemaker, and nodal rhythm during expiration, were observed

with approximately the same degree of frequency in the normal and the rheumatic group. The similarity of response in the two groups suggests that the prolongation of the conduction time which is occasionally found in rheumatic subjects with apparently normal hearts may be caused by increased vagal activity, rather than by a specific injury of the conduction system.

When an increase of 0.04 second, or more, in the conduction time occurs during the course of an acute rheumatic infection, it is interpreted as a definite sign of cardiac involvement; in a rheumatic child with no signs of rheumatic activity, it raises the suspicion that the rheumatic process is becoming active. On the other hand, a decrease in the conduction time in rheumatic children suggests that the myocardial lesions are healing.

In view of our observations that significant changes in the P-R interval may occasionally occur in normal, as well as in rheumatic, children, such changes, in the absence of other positive signs, should be interpreted with caution. Significant variations occurred not only in rheumatic children with prolonged conduction times who had no detectable signs of rheumatic activity, but were also occasionally observed in four rheumatic children whose P-R intervals were usually from 0.15 to 0.16 second.

It is our impression that no simple explanation of these phenomena is possible. The action of the vagus is extremely complex and varies not only with vagal tone, but also with the activity of the opposing (sympathetic) system. Furthermore, although it is thought that the cardiac impulse in each person usually follows the same path, this may not be true in every case. For instance, in cases of the so-called Kent conduction mechanism[14] there is evidence for the existence of more than one anatomic pathway. It seems possible that spontaneous fluctuations as striking as those which we observed in Case 8 (Table I) may be caused by the fact that the impulse travels by different pathways at different times.

CONCLUSIONS

1. The electrocardiograms of 150 *normal* girls, whose ages ranged from 6 to 16 years, were studied. The A-V conduction time was prolonged (to 0.19 second, or more) in eight, or 5 per cent, which is a higher incidence than has previously been reported.

2. The incidence (5.7 per cent) of prolongation of the A-V conduction time (to 0.20 second, or more) in a group of 140 *rheumatic* children with no detectable signs of rheumatic activity and no demonstrable evidence of organic heart disease was nearly the same as that among the 150 normal girls.

3. Occasionally, spontaneous variations in the P-R interval occurred, both in normal and rheumatic children with prolonged conduction times who had no detectable signs of rheumatic activity. An increase

in the P-R interval was also observed in four rheumatic children with an apparently inactive rheumatic infection whose conduction times were usually 0.15 to 0.16 second.

4. The effect of stimulating and inhibiting the vagus by exercise and holding the breath was studied on normal and rheumatic children with prolonged A-V conduction who showed no evidence of rheumatic activity. The results in the two groups were essentially the same and suggest that prolongation of the P-R interval in children with normal hearts may be the result of increased vagal activity, rather than specific injury of the conduction system. Our observations are in accord with those of Ferguson and O'Connell, namely, that prolongation of the P-R interval is not in itself a reliable index of myocardial involvement.

5. In the absence of other abnormalities, the clinical significance of an increase or decrease in the P-R interval in rheumatic children remains doubtful. Spontaneous variations in the A-V conduction time of normal persons have been reported by other workers, as well as by ourselves.

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THE INFLUENCE OF DIGITALIS ON THE ELECTROLYTE AND WATER BALANCE OF HEART MUSCLE

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The BENEFICIAL effect of digitalis in cardiac failure is usually[1] attributed to (1) vagal slowing of the heart rate, (2) a depression of conduction, particularly at the A-V node, and (3) a direct action on the myocardium, whereby its contractile power is augmented. The mechanism by which these actions are brought about still remains rather obscure.

Within recent years, extensive studies have been made[2, 3, 4] on the electrolyte and water balance of skeletal muscle during stimulation and recovery. The development of the chloride space concept[5, 6, 7] as a means of defining the intracellular and extracellular constituents has proved to be very valuable in these investigations. Since this concept has not been applied to heart muscle, it was considered advisable to use it to investigate the influence of digitalis on heart muscle.

In considering previous investigations bearing upon this subject, the observations made on heart muscle in cases of cardiac failure are of interest. Harrison, Cullen, et al.,[8, 9, 10, 11] found that in heart failure there are a reduction in muscle potassium and an increase in sodium and water content. They also observed a reduction in potassium in experimentally produced skeletal muscle fatigue. This latter observation has been confirmed by Fenn et al.,[4] and Tipton,[12] who applied the chloride space concept. It has also been shown[12] that both calcium and the adrenal cortex hormone act to reduce the potassium loss in stimulated skeletal muscle. Mangun and Myers[13] have confirmed the fact that there is a loss of potassium in cardiac failure, and they have observed that the degree of this loss is related to the extent of cardiac damage and hypertrophy. They also observed that the potassium loss was accompanied by a reduction in phosphorus and creatine and suggested that these three changes represented only different phases of the same problem. That there is a reduction in creatine and phosphorus in heart failure has been confirmed.[14] Zwemer and Truszkowski[15] have noted that the muscle fatigue which is so prominent a feature of adrenal cortical insufficiency is accompanied by a reduction in skeletal and also cardiac muscle potassium. Britton, Silvette, and Kline[16] have demonstrated that there is also a loss of glycogen from the muscles and liver in adrenal insufficiency, and they have suggested that potassium

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maintenance and glycogen maintenance within the cells are intimately related. The loss of potassium from the muscle cells in cardiac failure and skeletal muscle fatigue appears to have an important relation to the impairment of function and diminution of contractile power.

Previous studies on the effect of digitalis on the potassium content of heart muscle have not yielded entirely consistent results. In dogs, Calhoun and Harrison[17] observed a marked decrease in muscle potassium after toxic and fatal doses of digitalis and no significant change after therapeutic doses. Cattell and Goodell,[18] who used the excised frog sartorius, and Wood and Moe,[19] who studied isolated heart preparations, confirmed the observation that large doses of the drug caused loss of potassium. However, Wedd[20] reported that the therapeutic action of digitalis was not the result of a lowering of the potassium content, and that when potassium loss did occur it represented a late, toxic effect of the drug. Hagen,[21] further, found that calculated therapeutic doses of digitalis caused a uniform and significant increase in the potassium content of isolated rabbit hearts, whereas toxic doses produced a marked decrease in potassium.

METHODS

Twenty adult cats, nine controls and eleven digitalized animals, were used in this study. Cats were chosen because of the recognized similarity of their digitalis response to that of man. In preliminary experiments the rabbit was found to be extremely refractory to digitalis,[22] and the electrocardiographic effects of digitalis were rather inconsistent.

Aside from the administration of digitalis, the procedure of handling controls and digitalized animals was the same. Except in one instance, the cats were examined in pairs; one was a control, and the other a digitalized animal. They were anesthetized with sodium pentobarbital, given intraperitoneally, and electrocardiographic studies were made. The average doses of sodium pentobarbital (49 mg./kg.) in the two groups were practically the same, although some individual variability was found in the amount required to maintain satisfactory anesthesia. The total duration of the anesthesia was the same for both groups, averaging about three or four hours.

Immediately before killing the animals, blood was drawn for chemical analysis; the thorax was then opened, the heart was quickly excised, and samples of the left ventricular wall were taken. A portion which weighed approximately 1 to 1.5 Gm. was taken for analysis of the water, sodium, and potassium content, and two smaller samples were removed for determination of the chloride content. Large blood vessels, fat, papillary muscles, and the septum were avoided. For water content, the muscle was dried at 105° C. until its weight became constant. The dried muscle was then ashed in platinum crucibles in a muffle furnace, at 500° to 550° C. Sodium and potassium determinations were made, in triplicate, on aliquots of the ash, sodium by the uranyl zinc acetate method of Butler and Tuthill,[23] and potassium by the chloroplatinic acid method of Shohl and Bennett.[24] Chloride content was ascertained by the method of Van Slyke and Sendroy.[25] The same methods were used in analyzing the blood serum. In addition, the specific gravity of the serum was recorded. In twelve animals the total nitrogen content was ascertained by micro-Kjeldahl digestion; the nonprotein nitrogen content, by micro-Kjeldahl digestion and aeration of the trichloracetic acid filtrate; the total protein content, by the difference between total and nonprotein nitrogen; the total

calcium content, by the Clark and Collip modification[26] of the Kramer-Tisdall method;[27] and the ionized calcium content, by calculation according to the method of McLean and Hastings.[28] The extracellular water, or chloride space, and the intracellular water were calculated from the data by the method described for skeletal muscle by Fenn et al.[4]

The method of giving digitalis was varied slightly. Five of the eleven cats were digitalized on the day of the experiment by giving rather large doses of digifoline (Ciba) intraperitoneally. The experiment was stopped when the effect of digitalis on the electrocardiogram became definite. The other six cats were given digitalis over a period of two to five days, in a dose of approximately 0.5 cat unit per day for an average, 3-kilogram cat. We did not attempt to make an exact calculation of the dosage of digitalis in relation to body weight, for it has been found that the digitalis response of cats, like that of man, is variable, and not wholly proportional to body weight. The therapeutic dose of digitalis was taken to be the amount which would produce characteristic electrocardiographic changes, but no clinical or electrocardiographic evidence of intoxication.

TABLE I

MUSCLE	CONTROL CATS		DIGITALIZED CATS	
	MEAN	S. E.$_m$	MEAN	S. E.$_m$
H_2O Gm./kg. wet	768.9	±3.4	771.4	±2.1
Cl^- meq./kg. wet	*35.2*	±0.85	*31.67*	±0.46
Na meq./kg. wet	40.8	±2.27	41.8	±0.65
K meq./kg. wet	*61.5*	±2.01	*69.4*	±2.17
Extracellular H_2O Gm./kg.	*265.6*	±4.6	*243.5*	±2.9
Intracellular H_2O Gm./kg.	*503.3*	±5.9	*527.9*	±3.8
SERUM				
Specific gravity	1.026	±0.002	1.027	±0.002
H_2O Gm./kg.	914.2	±2.4	914.7	±2.1
Cl^- meq./Liter	120.4	±1.0	118.3	±1.0
Na meq./Liter	150.0	±2.7	149.0	±2.2
K meq./Liter	5.77	±0.45	5.26	±0.75
Ca^{++} meq./Liter	2.80	±0.05	2.76	±0.06
Protein per cent	5.7	±0.3	5.7	±0.4
Total Ca per cent	11.25	±0.4	11.02	±0.25

RESULTS

The results of the chemical analyses are given in Table I. The standard error of the mean was calculated by the usual formula. Differences between the means were related to the standard error of the difference in order to derive the probability of true significance. The means which were found to differ significantly are shown in italics.

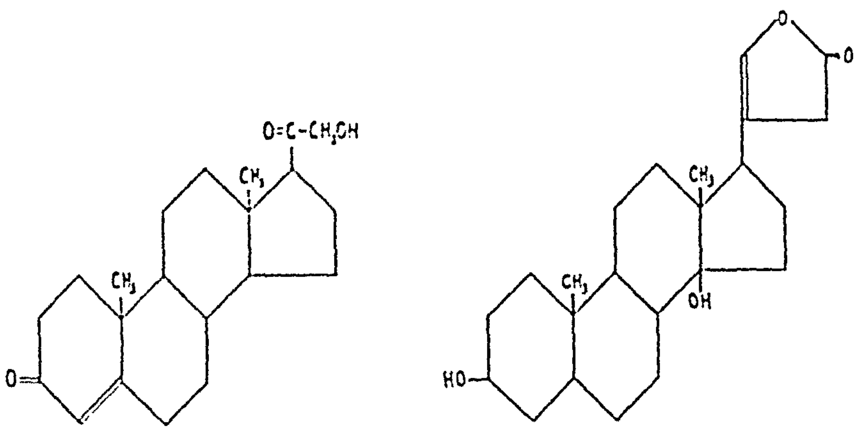
In this series of cats, the significant chemical changes caused by digitalization were an increase in potassium and intracellular water and a decrease in chloride and extracellular water. No other significant alterations occurred.

DISCUSSION

The concentration of the calcium ion in the serum was estimated because of the synergism which is known to exist between calcium and digitalis.[29] In dealing with a problem which involves the permeability of cell membranes to other electrolytes, calcium, because of its essential role in the formation and maintenance of protoplasmic membranes,[30]

must be considered. An appreciable variation in the calcium-ion concentration might conceal or exaggerate the effects of digitalis. Perhaps, also, digitalis might exert some of its effect by varying the calcium-ion concentration. However, as far as can be ascertained from this study, digitalis has no effect on the ionized calcium of the blood. The observed variability in ionized calcium may possibly explain some of the differences in the reaction of animals to calculated doses of digitalis.

Judging from the results of this study, we believe that the effect of digitalis on heart muscle appears to be quite like that of the adrenal cortex hormone, in that it acts to maintain the potassium within the cell. This action is accompanied by an increase in the hydration of the muscle cell. Both the skeletal muscle weakness caused by adrenalectomy and the myocardial weakness associated with cardiac failure are accompanied by a decrease in intracellular potassium; and the improvement in contractile power brought about by the administration of adrenal cortex hormone and digitalis, respectively, may be definitely related to the resultant restoration of potassium to the intracellular position, where its presence is essential for the maintenance of vital processes.



DESOXYCORTICOSTERONE DIGITOXIGENIN

Fig. 1.—The chemical structure of desoxycorticosterone is the same as that of the crystalline adrenal cortex hormones A and B, which were isolated by Kendall, with the exception that there is an O or OH at C_{11}. Digitoxigenin is the aglycone and active portion of digitoxin, and is similar in structure to the aglycones of all the digitalis group of cardiotonic drugs.

The striking similarity in chemical structure between digitalis and the adrenal cortex hormone (Fig. 1) also suggests that they may have similar actions. It has been supposed by Zwemer and Truszkowski,[15] and others, that the action of the adrenal cortex hormone is related to differential permeability of cell membranes. The fact that calcium has a cell membrane role suggests that digitalis may act similarly. Recently, Zwemer and Lowenstein[31] have found that digitalis glucosides lower plasma potassium levels and prolong life in adrenalectomized animals;

this is a systemic action like that of the adrenal cortex hormone. The plasma potassium levels in our digitalized animals were slightly lower than in the controls, although, by the usual standards, the difference was not statistically significant. Further investigation will be needed to demonstrate the extent to which digitalis may or may not be substituted for the adrenal cortex hormone. However, it seems probable that digitalis exerts a cortin-like action directly on the heart muscle.

CONCLUSIONS

The electrolyte and water balance of heart muscle was studied in twenty cats. In this series, therapeutic doses of digitalis produced a significant increase in the intracellular potassium and intracellular water content of the heart muscle. The amount of chloride and extracellular water was reduced.

It is suggested that the beneficial effect of digitalis in cardiac failure may be brought about, in part, by a cortin-like action upon the myocardium, whereby potassium is maintained within the cell and cell hydration is improved. This may be caused by an alteration in the permeability of the muscle cell membrane to electrolytes.

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THE SIGNIFICANCE OF THE POSITION OF THE SUBJECT IN THE EVALUATION OF THE ELECTROCARDIOGRAM

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ALTHOUGH it has been recognized since the early days of electrocardiography that the form of the tracing is influenced by the position of the subject, no uniform technique has been adopted. In many instances, individual practice is determined by the facilities at hand; one of the most important considerations is space limitation, which favors the sitting position. However, in other cases it is probable that the position of the subject is a matter of chance, especially if the significance of differences in configuration which occur when the position of the subject is varied is not appreciated. The fourth edition of "Nomenclature and Criteria for Diagnosis of Diseases of the Heart" takes cognizance of the potentialities of the situation and suggests that the position of the body at the time of making the record be stated in the report. There is, however, no statement as to which position is to be preferred.

We have been interested in observing the effect of position on the T waves, as it is our feeling that erroneous diagnostic conclusions result most frequently in this connection. The literature dealing with this problem is not extensive and tends to concern itself more with attempts to explain positional variations on anatomic and physiologic grounds than with the establishment of an optimum technique. Schlomka and Reindell,[1] in their investigation of the effect upon the electrocardiogram of changing from the recumbent to the standing position, found that the T wave became less positive and, in many instances, related this to diminished cardiac reserve. They feel that this phenomenon may be used as a basis for a diagnostic test, stating that the changes tend to regress in favorable cases and to persist in the presence of impaired function. They do, however, mention the advisability of adopting a universal technique of making tracings with the subject recumbent. Leimdörfer[2] discusses positional changes in cases of latent disease and considers such changes of diagnostic importance. He regards this variability as the result of physiologic alterations in coronary blood flow. Hinrichs[3] believes that electrocardiograms made with the subject in the standing position permit one to evaluate functional changes in individual parts of the heart, and that the act of standing will render the effects of myocardial disease more apparent. He states that only minor

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positional variations occur in normal subjects, but he mentions specifically the fact that the assumption of the erect posture reduces the amplitude of the T wave.

Katz and Robinow,[4] on the other hand, maintain that changes in the position of the heart within the chest account for the variations in the electrocardiogram which occur with the shift from the recumbent to the upright position. Contributing factors are said to be rotation about various axes, displacement of the heart as a unit without rotation, and alteration in the contour of the chest cavity. The summation of these factors produces essential variations in the electrical field of the body, and changes in the configuration of various complexes result. Sanders[5] reported a case of marked postural hypotension in which changes in the electrocardiogram accompanied the fall in blood pressure which occurred with assumption of the upright position. The T wave was positive when the patient was recumbent, but it became diphasic when he stood up. Åkesson[6] emphasizes the role of "orthostatic anemia" in producing T-wave changes and discusses the influence of position, vagosympathetic balance, and alterations in coronary flow; he thinks that the last factor is the most important. Janzen,[7] although he confirmed the fact that the T wave changes in the direction of left axis deviation, observed a tendency, in most cases, toward a return to the original form when the standing position was maintained for several minutes. He interprets this observation as indicating that functional factors, as well as changes in the position of the heart, influence the configuration of the T wave. He points out, also, that positional changes appear more rarely and are less prominent in cases of cardiac disease and are not as common in older people as in young persons with labile vasomotor systems. He believes that, although no rule can be established, the most extreme T-wave changes occur when there is pronounced orthostatic tachycardia. He does not believe that a functional test can be based on the positional variations under discussion. Erkelens,[8] who found these changes in a number of healthy persons, concurs in this belief and expresses the opinion that body build has a distinct influence; the most marked variations occur when the subject is of the asthenic type. Korth,[9] although he did not emphasize positional changes, observed variable T waves under different conditions and noted that exertion had an effect in some cases. He also stressed the fact that persons with an unstable vasomotor system are most likely to show variations in the T waves.

Sigler[10] described T-wave alteration with changes in position in thirty-three normal subjects; he compared the recumbent with the standing postures, but he pointed out that changes also occur with the assumption of the sitting position. He aptly observes that the changes in some cases are so marked as to make the electrocardiogram appear abnormal and lose its identity with tracings taken in other postures.

He supports the view of Katz and Robinow in regard to the influence of adjacent structures; the T-wave changes are supposedly caused by differences in the mode of spread and retreat of the current. He also takes issue with those who would use positional changes to evaluate cardiac function.

Our interest in the problem was awakened by the discovery, in a group of apparently healthy young subjects, of T-wave changes in Leads II and III which could not be regarded as within the usually accepted normal limits. When careful cardiovascular examination failed to disclose any evidence of organic cardiac disease, further electrocardiographic studies, with special reference to the influence of position, were undertaken. In every instance, the tracings which were made with the subject in the recumbent position were entirely normal as regards T-wave configuration. In some cases, the assumption of the upright position rendered the T waves negative in Leads II and III, and many subjects had diphasic or practically isoelectric T waves in Lead II, and negative T waves in Lead III. Assumption of the recumbent position invariably produced, in Lead II, positive T waves of normal configuration and amplitude. Changes in Lead III were less constant and not so marked. An incidental observation was that, in most instances, recumbency rendered the base line more even. Eight subjects showed moderate to marked somatic tremor in the upright position, but little or none in the recumbent posture.

Having conclusively established these facts with regard to the effect of position, we extended our study by making records in the sitting and recumbent positions in every case in which there was even a suspicion of changes in the S-T segment and T wave in Leads II and III. We found that positional variation occurred invariably in our normal subjects. It also became apparent that those who showed these changes were usually young and of slender build; many were highly nervous, and, although we could find no evidence of organic heart disease, they clearly showed the characteristic signs of vasomotor imbalance. In no instance was there a sufficient change in blood pressure to warrant a diagnosis of orthostatic hypotension, and none of the subjects had complaints which suggested this condition.

In thirty-seven cases there were T-wave configurations in the original records, made when the patient was in an upright position, which warranted a suspicion of myocardial involvement of some type. In no case, after repeated examinations, was evidence of organic heart disease found. Thirty-two of these subjects were 29 years of age, or less, and five were 30, or more. There were sixteen males and twenty-one females. Twenty-five weighed ten or more pounds less than would be expected for their age and height.

Table I outlines the salient clinical features in each case, together with the relevant T-wave changes which occurred with change of position. In all but four cases, the heart rate slowed when the subject lay down, and, in eleven, the rate retardation exceeded 20 beats per

minute. Definite deviation of S-T or T-P from the isoelectric line was noted in nineteen cases. Unless otherwise stated, there was a slight QRS shift toward right axis deviation when the upright position was assumed, but the QRS changes were insignificant in all cases. It should be mentioned that in some cases the degree of positional variation later diminished, probably because the vasomotor system became more stable with increasing age. Added weight may also have been a factor.

Figs. 1 and 2 were selected from our series to illustrate striking T-wave variation with change of position.

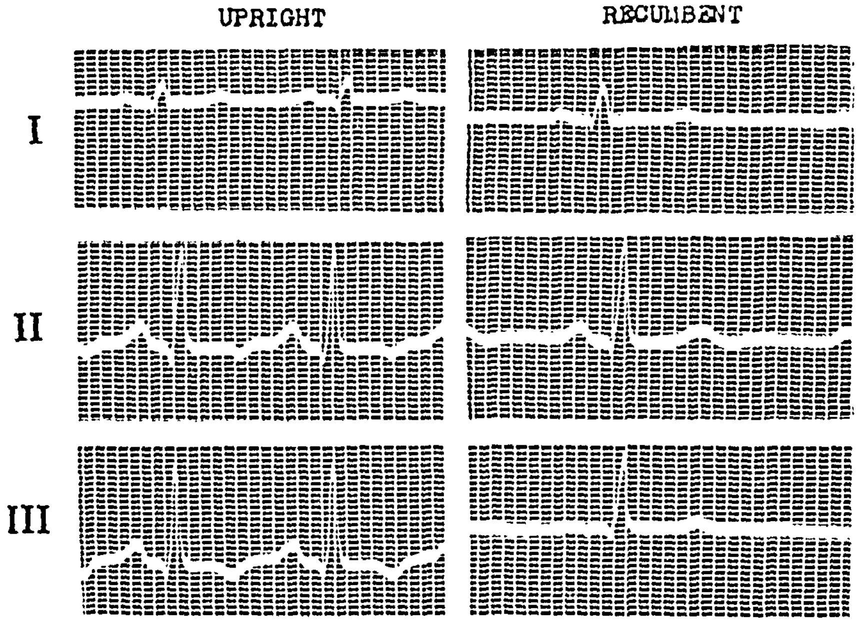

Fig. 1.—Case 5. The T waves in Leads II and III become upright in recumbency, the rate is much slower, and TP elevation is eliminated.

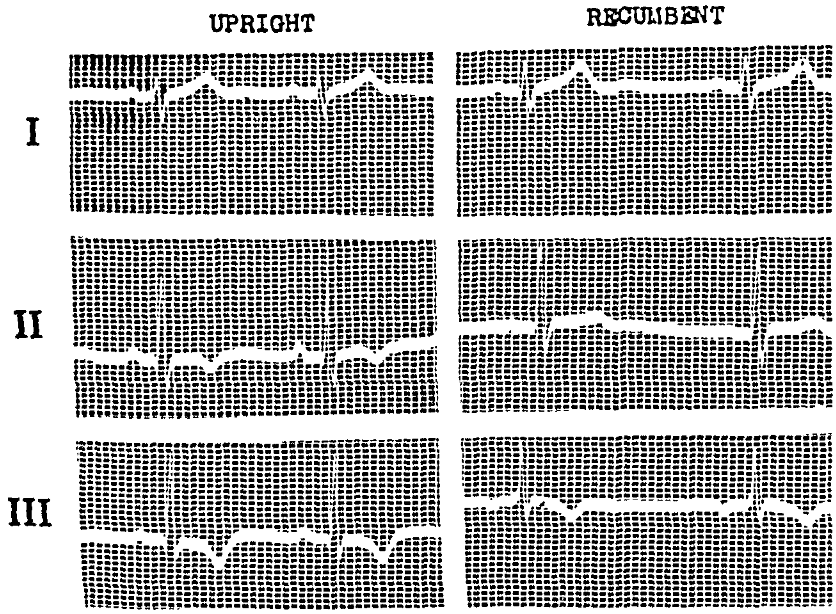

Fig. 2.—Case 33. The T waves in Lead II become upright in recumbency, with appreciable slowing of rate.

TABLE I

CASE NUMBER	RECORD NUMBER	AGE	SEX	HEIGHT	WEIGHT	DEVIATION FROM AVERAGE BUILD*	ELECTROCARDIOGRAM WITH SUBJECT UPRIGHT					ELECTROCARDIOGRAM WITH SUBJECT RECUMBENT					REMARKS
							RATE	S-T	T-P	T_2	T_3	RATE	S-T	T-P	T_2	T_3	
1	1934	26	M	5′ 11″	135	−26	96	iso.	+1, L_2	+.5	+1	80	iso.	iso.	+1.5	+1.5	
2	2368	28	F	5′ 1″	99	−22	110	−.5, L_2	+1, $L_{2,3}$	diph.	diph.	86	iso.	iso.	+3	+1	
3	2579	19	F	5′ 7″	138	+ 3	102	iso.	+.5, L_2	+1	−1.5	85	iso.	iso.	+2.5	+.5	
4	2585	22	M	5′ 11″	140	−18	70	iso.	iso.	+.5	−1	65	iso.	iso.	+1.5	diph.	
5	2602	19	M	5′ 11″	134	−23	100	iso.	+1, $L_{2,3}$	−1	−2	72	iso.	iso.	+2	+1	
6	2616	22	M	5′ 10″	135	−19	90	iso.	iso.	+1.5	−1.5	86	iso.	iso.	+2.5	−1	
7	2650	19	F	5′ 4″	118	− 6	94	iso.	+.5, L_2	diph.	−1	94	iso.	iso.	+1.5	−.5	
8	2967	28	M	6′ 4″	156	−37	82	iso.	iso.	+.5	−1	65	iso.	iso.	+1.5	−1.5	T_1: +1 U, +2.5 R
9	2985	18	M	5′ 11″	126	−27	92	iso.	iso.	−1	−3	70	iso.	iso.	+2	−1	
10	2992	23	F	5′ 3″	142	+18	86	iso.	iso.	+.5	−1	75	iso.	iso.	+1.5	−.5	
11	3005	32	M	5′ 7″	112	−37	100	iso.	+1, L_2	+1	−2	82	iso.	iso.	+3	+.5	Somatic tremor U
12	3011	25	M	6′ 0″	176	+ 9	100	iso.	iso.	−.5	−1	78	iso.	iso.	+1	−1	Somatic tremor U
13	3020	24	M	6′ 1″	145	−26	112	iso.	+1, L_2	+1	−.5	96	iso.	iso.	+2	+.5	
14	3055	26	F	5′ 8″	118	−25	90	−1, L_2	+.5, L_2	+.5	−2	72	iso.	iso.	+3	+1	
15	3169	26	M	5′ 8″	135	−15	100	iso.	iso.	iso.	−.5	84	iso.	iso.	+1.5	+.5	
16	3234	23	F	5′ 3″	110	−14	102	−.5, L_2	iso.	+1	iso.	88	iso.	iso.	+2	+.5	Somatic tremor U
17	3238	18	F	5′ 6″	134	+ 4	76	−.5, L_2	iso.	+1	−1.5	72	−.5, L_2	iso.	+2	−.5	
18	3258	22	F	5′ 3″	120	− 3	96	iso.	iso.	diph.	−1	78	iso.	iso.	+1	−.5	
19	3281	23	M	6′ 2″	163	−12	100	iso.	iso.	+.5	−1	96	iso.	iso.	+2	diph.	
20	3327	18	F	5′ 3″	93	−27	110	−.5, L_2	+.5, L_2	diph.	diph.	88	iso.	iso.	+1	iso.	T_1: diph. U, +.5 R

21	3337	68	M	5′ 10″	177	+ 4	100	iso.	iso.	iso.	iso.	96	iso.	iso.	+2	+.5	T_1: +.5 U, +2 R
22	3341	22	M	6′ 0″	166	+ 3	88	+.5, L_2	iso.	+.5	–.5	68	iso.	iso.	+1	diph.	Somatic tremor U
23	3360	31	F	5′ 5″	135	+ 0	92	iso.	iso.	iso.	–.5	85	iso.	iso.	+1.5	–.5	QRS axis toward left U
24	3375	21	F	5′ 4″	111	–15	106	iso.	+1, $L_{2,3}$	diph.	–1	96	iso.	+1, L_2	+2	diph.	Somatic tremor U
25	3382	30	F	5′ 9″	140	–10	102	iso.	+.5, L_2	diph.	–1	75	iso.	iso.	+2	iso.	
26	3388	25	F	5′ 4″	114	–14	72	iso.	iso.	+.5	–.5	72	iso.	iso.	+1.5	diph.	
27	3422	20	F	5′ 6″	120	–12	100	iso.	+.5, L_2	+1	diph.	74	iso.	iso.	+2	+1	
28	3430	24	M	5′ 11″	146	–14	88	iso.	iso.	iso.	–1	88	iso.	iso.	+2.5	+1	
29	3438	36	M	5′ 9″	144	–17	88	iso.	iso.	iso.	–1.5	65	iso.	iso.	+2	–.5	QRS axis to left U
30	3459	26	F	5′ 3″	106	–19	92	iso.	+1, L_2	+1.5	diph.	62	iso.	iso.	+2.5	+1.5	Somatic tremor U
31	3465	25	F	5′ 0″	100	–17	76	iso.	iso.	+.5	–1.5	76	iso.	iso.	+2.5	–1	Somatic tremor U
32	3473	19	F	5′ 1″	112	– 3	96	iso.	+1, L_2	+1.5	iso.	84	iso.	iso.	+2.5	iso.	Somatic tremor U
33	3500	20	M	6′ 0″	139	–22	76	iso.	iso.	–1.5	–4	52	iso.	iso.	+1	–3	
34	3599	20	F	5′ 5″	103	–25	106	iso.	iso.	+.5	–1	86	iso.	iso.	+2	+1	
35	3833	20	F	4′ 11″	96	–16	102	–.5, L_2	iso.	diph.	–1	90	iso.	iso.	+2	diph.	
36	3884	18	F	5′ 5″	122	– 4	110	iso.	+.5, L_2	+.5	–1	84	iso.	iso.	+2	–.5	QRS axis toward left U
37	3890	19	F	5′ 2″	117	– 1	110	iso.	iso.	iso.	diph.	83	iso.	iso.	+2	diph.	

*Medico-Actuarial Mortality Investigation of 1912.
+ and – values refer to positive and negative deflections in mm., 1 cm. representing 1 millivolt.
L_2 and L_3, under S-T and T-P, refer to the respective leads in which deviations from the isoelectric line occurred.
iso. = isoelectric; diph. = diphasic; U = upright; R = recumbent.
Height in feet and inches. Weight in pounds, with clothing.

DISCUSSION

Judging from our observations, we believe that all electrocardiograms should be made with the subject in the reclining position. Not only would this eliminate the possibility of making certain diagnostic errors, but heart rates would be slower, and this would tend to diminish the S-T and T-P distortion which is often incident to tachycardia. Another fact of importance is that, in most cases, the base line is more even when the subject is recumbent. There have come to our attention no reasons, except that of expediency, why the sitting position should be used. In view of the conflicting statements in the literature and the observations on normal persons which we have presented, the use of positional changes to evaluate functional capacity does not seem justified.

CONCLUSIONS

1. In a series of thirty-seven normal subjects, marked changes in T-wave configuration were produced by altering the position of the body. The possibility that this may lead to diagnostic errors is emphasized.

2. The adoption of a standard electrocardiographic technique, to include the making of all tracings with the subject in the recumbent position, is advocated.

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CHROMATROPHIC DEGENERATION AND RUPTURE OF THE AORTA FOLLOWING THYROIDECTOMY IN CASES OF HYPERTENSION

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SPONTANEOUS rupture of the aorta is not an extremely rare condition. Although it was formerly believed to be caused by arteriosclerotic and syphilitic lesions, more recent studies indicate that it can occur in an aorta which appears normal grossly, and presents little or no evidence of arteriosclerosis.[1-6] Erdheim[7] was the first to discover microscopic changes of a specific type which he designated as cystic degeneration. Other forms of degeneration have since been reported. Roberts,[8] in a recent paper on cystic degeneration of the aorta, reported a single example of the condition and was able to collect twenty-seven authentic cases from the literature. In the three cases which are to be reported, the ruptured aorta was the seat of degeneration of the muscular coat typical of that described by Erdheim.[7] In each instance a thyroidectomy had been performed before the rupture occurred, and all of the patients were suffering from severe, chronic hypertension. The clinical manifestations in these three cases were so strikingly similar that, although the possibility of coincidence could not be excluded, the events are worthy of record.

REPORT OF CASES

CASE 1.—N. K. was a thirty-nine-year-old woman who first entered Barnes Hospital on the surgical service. The complaints at the time of admission were smothering spells, dyspnea, palpitation, nervousness, fine tremor of the hands, and fatigability. These symptoms had become troublesome early in 1934. When she first consulted her physician, Feb. 20, 1934, her blood pressure was 230/130. She was kept in bed one month, without improvement. Her basal metabolic rate was found to be plus 39 per cent. Examination of her urine revealed a trace of albumin and occasional granular casts. The physician made a diagnosis of thyrotoxicosis, hypertension, cardiac hypertrophy, and nephritis. She was instructed to rest from February until May, and to spend at least eighteen hours in bed each day. During this period her blood pressure did not change, and she was advised to enter Barnes Hospital. Examination at that time showed a moderate amount of orthopnea and some dyspnea on exertion. Her eyes were prominent, but there was no lid lag. Examination of the eye grounds revealed a hypertensive retinitis, with some distention of the veins and slight papilledema. The retinal vessels were tortuous, and hemorrhages and scarring were evident. The heart was enlarged to the left, and the heartbeat was rapid and regular. The aortic second sound was accentuated and had a ringing

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quality. No murmurs were noted. The blood pressure was 220/160. Her vital capacity was only 1,600 c.c. The basal metabolic rate shortly after admission was plus 73 per cent. The following day it was plus 46 per cent. Tests revealed that her kidneys had preserved the ability to concentrate urine. A faint trace of albumin, with occasional hyaline casts, was found. The nonprotein nitrogen content of the blood was normal. The patient was believed to have a malignant type of hypertension, with an increase in her basal metabolic rate. Although it was considered that the hypertension was not the cause of the thyrotoxicosis, the signs and symptoms, as well as the increased basal metabolic rate, suggested that the patient's condition might be improved by removal of the thyroid gland. In view of the rapid heart rate, dyspnea, edema, and early cardiac disease, and because at that time complete thyroidectomy was regarded as beneficial in cases of long-standing cardiac failure, it was suggested that the entire thyroid gland be removed; this was done on June 8, 1934. Convalescence was uneventful, and the patient was greatly pleased with the result of her operation. She was discharged after fourteen days of postoperative observation. The shortness of breath, nervousness, and orthopnea were diminished.

On Oct. 3 she re-entered the hospital for an examination. She had had no smothering spells and no fatigue, except that she felt weak upon climbing stairs. She was no longer troubled with dyspnea. Her weight had increased. The essential features noted at this examination were obesity, coarseness of the voice, and pitting edema of the extremities. Her blood pressure was 210/140. Her basal metabolic rate was minus 7 per cent. Examination of the eye grounds showed marked improvement. The papilledema had disappeared, although the margins were still indistinct. It was stated that the vessels appeared less tortuous, that the scars of old hemorrhages had not increased, and that no new hemorrhages were apparent.

During the next two months she was up and about for the greater part of each day, but did not work. On Nov. 8, five months after operation, she went with her husband, after dinner, for a ride in the car. He left her for a few minutes to get cigarettes in a drug store. When he returned he found her gasping for breath. He started for the hospital, which was only a few blocks away, but before he could reach it she was dead.

Autopsy (Washington University No. 5921, performed by Dr. P. Kunkel) revealed a short, obese, white woman of an hypersthenic habitus. The eyes appeared prominent. There was a transverse thyroidectomy scar in the lower part of the neck. The face was not hirsute, but the chest and breasts below the nipples were covered with coarse, black hair. The external genitalia were normal. The skin was smooth and soft. The distribution of fat seemed to be of the simple type, and was not suggestive of endocrine dysfunction. The subcutaneous tissue was increased in amount. The peritoneal cavity contained 100 c.c. of clear fluid. The left pleural cavity was filled with a clot of 300 c.c. of blood, and a small amount of serum. There was a small hemorrhage beneath the epicardium at the tip of the right auricle. The upper mediastinum was infiltrated with blood. The adventitia of the aorta was red and hemorrhagic. Dissection of the neck failed to reveal any thyroid tissue. The heart weighed 800 grams. The hypertrophy was chiefly of the left ventricle. The myocardium was firm. Except for slight thickening of the mitral valve along the line of attachment of the chordae tendineae, the valves and endocardium were normal. Numerous atheromatous plaques were distributed throughout both coronary arteries. Microscopic examination of the heart showed marked hypertrophy of the muscle cells. There was no interstitial fibrosis. The coronary vessels showed extreme thickening, with some atheromatous change at various points. The muscular walls of the blood vessels

beneath the thickened areas of the intima were slightly atrophic. There was a slight perivascular infiltration of lymphocytes in the epicardial fat.

The wall of the ascending aorta was thin, and there were little atheromatous change and no wrinkling of the intima. Just above the posterior cusp of the aortic valve there was a small, jagged tear, 1 cm. in length. The vessel wall surrounding the tear was separated into two layers. The laceration extended completely through the wall, which had allowed blood to escape into the upper mediastinum and pericardial sac. The arch and descending portions of the aorta showed no gross changes. Several sections of the aorta around the tear and at more distal points were taken for microscopic study. At the point of the tear the aortic wall was separated into two layers.

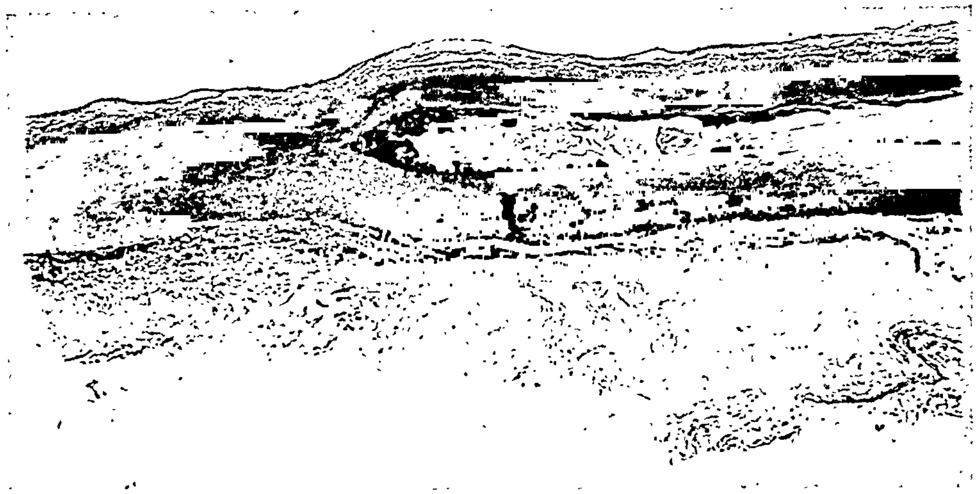

Fig. 1.—Photomicrograph (low power) of the dissecting aneurysm, showing the muscle layers split into two separate divisions. The thinner portion is toward the intimal layer.

The outer layer was composed of the adventitia and, in some places, a thin strip of media. The inner layer was formed by the intima and the greater portion of the media. A false channel extended within a short distance of the aortic ring. The most striking change in the vessel wall was the interstitial accumulation of faintly basophilic material between the elastic fibers, muscle fibers, and in the connective tissue. In several places just beneath the intima there were small areas in which muscle and elastic fibers had disappeared. Evidence of proliferation of fibroblasts was seen in only one of the areas of degeneration. The separation and degeneration of elastic muscle fibers were most marked in the inner half of the media. The interstitial material stained intensely with the metachromatic dyes. An increased amount of calcium could not be demonstrated with alizarin. The other sections, taken from various levels of the aorta, showed the same chromatrophic interstitial change, but to a less degree, and separation of the fibers was consequently less pronounced. Cyst formation was not seen in the arch and descending aorta. In some places, the elastic fibers appeared swollen and thickened, and were occasionally broken.

The Fallopian tubes were completely obliterated, and the ovaries contained simple cysts.

The remainder of the organs were essentially normal, except for the kidneys and adrenal glands. The latter weighed approximately 12 Gm. The left adrenal was thickened and nodular, and, on section, was found to contain several nodules, the largest of which measured 1 cm. in diameter. In the right adrenal there

was one small cortical nodule. Microscopic study of the adrenals showed that the nodules were composed of large, lipoid-rich, cortical cells which lacked the cord-like arrangement of the normal adrenal cortex. In many places the groups of cells were separated by dilated blood channels. The arteries in the cortex had extremely thickened walls. The right kidney weighed 150 Gm., and the left, 140 Gm. Their capsular surfaces were finely granular, and the cortex of each kidney was of approximately normal thickness. Dark-red spots were seen on the surface under the capsule, and the renal pelves were injected and thickened and likewise contained numerous small petechiae. Microscopically, the surface of the kidney was irregular because of arteriosclerotic scars. The capsule was thickened and hyalinized, particularly over the scarred areas. The walls of the small vessels were greatly thickened and hyalinized. There was some congestion of the glomeruli, but no hyalinization.

CASE 2.—H. C., a man of twenty-eight, first entered Barnes Hospital in August, 1935, with complaints of numbness of his right side and inability to focus his eyes. This had been noted three weeks before, while at work, and at that time had lasted four hours. He stated that, nevertheless, he finished his day's work, and then consulted a physician, who told him he had high blood pressure, with disease of the heart and kidneys. He told us that he had had two attacks of scarlet fever before the age of twelve. He had also had diphtheria at the age of ten, and rheumatism at the age of twenty and twenty-two. Examination revealed a man of relatively youthful appearance, with a flushed face and moderate emaciation. Examination of the eye grounds disclosed slight thickening of the arterial walls, with moderate tortuosity of the vessels; there were no exudates or hemorrhages. The tonsils were large, and pus could be easily expressed from the right one. The thyroid isthmus was enlarged. The heart rate was 120, and the heartbeat was regular. There were an apical systolic murmur and moderate cardiac enlargement. A fine, intense tremor was evident in the extended hand. The peripheral arteries were thickened. His blood pressure averaged 195/122. The basal metabolic rate on two occasions was plus 34 per cent and plus 32 per cent, respectively. The urine was normal. The concentration diuresis test showed an ability to concentrate to a specific gravity of 1.020. The phenolsulphonephthalein excretion was 45 per cent in two hours. The blood Kahn reaction was negative. Because of his infected tonsils and the urging of the consulting otolaryngologist, a tonsillectomy was performed. He returned to his physician, who gave him Lugol's solution and kept him in bed. His condition was not improved. He noted occasional shortness of breath, pounding of his heart, and, later, dizziness and transient attacks of amblyopia. His blood pressure rose to 210/135. During this interval the basal metabolic rate had been continuously high, but, on one occasion, was as low as plus 7 per cent. In May, 1936, because of his lack of improvement and the signs of increasing circulatory difficulty, he entered the hospital for a complete thyroidectomy. Following the operation his basal metabolic rate fell to minus 8 per cent. For three weeks after discharge he was given small doses of thyroid (½ gr. per day). This was discontinued because of rapidly rising blood pressure. Early in July he entered the hospital because of repeated, clonic convulsions which had occurred over a period of a week and were accompanied by headache, nausea, and vomiting. Ophthalmoscopic examination showed blurring of the disc margins, narrowing of the arteries, and exudate. His heart was enlarged to the left and downward. A rough systolic murmur, which had not been evident on the first admission, was heard at the apex. The blood pressure was 280/160. The basal metabolic rate was minus 5 per cent, but because of his serious condition it was questionable whether this represented the true value. After a few days' observation he returned home, but re-entered the hospital in October, 1936, five months after the operation, with

the complaint of violent precordial and substernal pain. His pulse was regular and not rapid; there were occasional dropped beats. A long, loud murmur, rough in quality, was heard at the base of the heart. A little later, auricular fibrillation became evident, with a large pulse deficit. His blood pressure was about 240/120. He died a few hours after admission.

Autopsy (Washington University No. 6637, performed by Dr. R. Elliott) revealed a well-developed, well-nourished white man. Except for a transverse thyroidectomy scar in the lower part of the neck, the appearance of the body was not unusual.

The left pleural cavity contained 250 c.c. of clear, straw-colored fluid. There were a few fibrous adhesions at the apex of the lung. The right pleural cavity was completely obliterated by fibrous adhesions.

The pericardial sac contained about 500 c.c. of clotted blood. The clot extended into the superior part of the mediastinum, where the upper part surrounded the proximal portions of the great vessels of the neck. When the heart was raised from its cavity, blood gushed from a large opening in the ascending aorta. The surfaces of the pericardial cavity were normal.

The heart weighed 500 Gm. The left ventricle was markedly hypertrophic. The right ventricle was of normal size and capacity. The left atrium was small, and the endocardium was thickened and opaque. There was a large, irregular hemorrhage in the interauricular septum, which was visible on the endocardial surfaces of both atria. The mitral valve and chordae tendineae were thickened. As a result of the thickening, the position of the valve was fixed, and the atrioventricular orifice was narrow. The other valves appeared essentially normal, although the aortic valve was slightly thickened. The coronary vessels arose about one centimeter above the free margin of the aortic valve. The orifice of the right coronary artery was greatly narrowed by an atheromatous plaque in the intima of the aorta. Beyond this point, the lumen of the vessel was not constricted. The left coronary vessel showed only occasional arteriosclerotic plaques. The myocardium of the left ventricle contained many fine gray foci, particularly in the papillary muscles. Microscopically, the muscle fibers of the left ventricle were greatly hypertrophied. For the most part they were widely separated. There was little interstitial fibrosis, but a considerable increase in the amount of perivascular fibrous tissue, which was not, however, arranged in a concentric manner. The mitral valve was composed of dense, fibrous tissue. Small vessels were found deep in the substance of the valve. Around one of the vessels there were concentrically placed epithelioid cells. There was no cellular infiltration elsewhere in the valve. The coronary artery showed some intimal proliferation, with atheromatous change in the thickest portion.

There was a long, linear tear in the posterior wall of the aorta, measuring 13 cm. in length. The tear began two centimeters to the right of the orifice of the left coronary artery and followed the course of the arch of the aorta, passing posterior to the great vessels. The edges of the laceration were generally smooth. There were a few, small, elevated atheromatous plaques in the intima adjacent to the lesion. The tear did not extend completely through the wall, but led into an extensive dissecting aneurysm which reached from the aortic ring to the renal arteries. The aneurysm at no point completely surrounded the aorta, but formed an irregularly shaped channel involving one-quarter of the circumference.

The channel assumed a spiral course (since it arose in the posterior part of the ascending aorta), became superior to the true lumen in the arch, was on the left in the descending portion of the aorta, and terminated in the anterior portion of the wall of the abdominal aorta. The false lumen followed the course of the celiac and renal arteries for a short distance. The walls of the aneurysm had a rough appearance. The blood within the channel was not clotted. The intima of the

aorta contained numerous, small, soft, atheromatous plaques, none of which was calcified or ulcerated. The intervening portions of the intima were smooth and yellow-tan in color. The aortic wall felt soft and inelastic.

Microscopically, the aorta showed the same lesion which was present in the first case. The essential change consisted of an increase in the amount of chromatrophic interstitial material, with resultant separation of the elastic membranes and muscle fibers. The distribution of the interstitial material was more uniform than in Case 1. In some sections, particularly in those from the ascending aorta, the muscle and connective tissue cells appeared degenerated, although large areas of tissue destruction and cyst formation were seen. Small cystic lesions, however, were frequently observed. In these regions, as well as elsewhere, the interstitial material stained intensely with metachromatic dyes, polychrome methylene blue, and toluidin blue. Sudan III and Scharlach R showed that there were small lipoid droplets in this substance.

The false channel lay in the outer half of the media in the ascending aorta, but in the descending portion it separated the vessel wall into two more or less equal parts. Fibrin and clotted blood were adherent to the walls of the channel. The tissues adjacent to the false lumen were infiltrated with inflammatory cells, chiefly polymorphonuclear leucocytes. The inflammatory change just described was confined to the media. It was patchy in distribution and most marked in the ascending aorta. The adventitia did not show fibrous thickening or perivascular infiltration. In places in which it lay close to the lumen, the tissue was infiltrated with inflammatory cells. The intima had undergone some arteriosclerotic thickening, with fatty change.

Fig. 2.—Photomicrograph (low power), showing a point of complete rupture of the aorta. The intimal surface shows no gross arteriosclerotic changes. Although, in the gross, the tear through the vessel appeared sharp, under the microscope it was quite irregular.

Nothing of importance was found in any other organs except the kidneys, which had a combined weight of 325 Gm. They were alike in size and shape. The capsules were densely adherent to granular surfaces. The cortex of each kidney was normal in thickness, but the architecture was considerably distorted by the irregular fibrosis. The pelves and ureters appeared normal. The arteries in the kidneys showed marked change. The walls of the arterioles were greatly thick-

the left coronary artery showed marked intimal proliferation, with slight fatty change. The muscle fibers in the media of the vessel were separated by interstitial material which was similar to that in the aorta in the other cases, but was much less in amount. Some of the small arterioles were markedly thickened.

About 1 cm. above the free border of the aortic valve there was a transverse tear in the posterior wall of the aorta. This laceration measured 2 cm. in length. At the right border it was continuous with a shorter tear which made a right angle with the larger laceration. Upon superficial inspection the edges of the laceration seemed as smooth as if they had been cut with a knife. No arteriosclerotic plaques or other lesions were present in the arterial wall. The wall of the aorta appeared to be unusually thin. The opening in the wall led directly into the pericardial sac. There was also a small amount of clotted blood about the branches of the pulmonary arteries. Microscopic examination of various levels of the aorta was made. The essential change in each case was the interstitial accumulation of an amorphous, basophilic material between the muscle fibers and elastic fibers of the media. The amount and staining properties of this material varied with each section. The largest accumulations were found in the ascending aorta, just anterior and to the right of the laceration. Here the fenestrated elastic membranes and muscle cells were so separated by the interstitial material that at times they could scarcely be identified. In several places, in the outer half of the media, they had disappeared altogether, with the formation of small, irregularly shaped cysts. The interstitial material stained faintly with hematoxylin and was structureless except for occasional, fine fibrils. Elsewhere, even in the wall adjacent to the laceration, the interstitial material was not so plentiful, but stained more deeply with hematoxylin, as well as with the metachromatic dyes. The elastic membranes were widely separated and were broken and frayed.

The nuclei of the muscle cells were normal. The interstitial change was more marked in the inner half of the aortic wall. The interstitial material stained with basophilic dyes, as well as metachromatic stains, polychrome methylene blue, toluidin blue, methylene blue, etc.

The intensity of the metachromatic reaction in this case seemed to vary with the size of the accumulation. The larger patches appeared more serous and hence less mucoid. The Sudan III and Scharlach R stains could be demonstrated in the interstitial chromatrophic material. Alizarin failed to reveal deposits of calcium. There was no evidence of an inflammatory reaction or of efforts at repair in any section. The intima in most of the sections showed no change, although there were fat droplets in the cells underlying the endothelium. The intima immediately adjacent to the laceration was entirely normal. In the sections from the descending portion of the arch there were a few atheromatous plaques which presented the usual appearance. The adventitia was not thickened, but contained numerous erythrocytes. The vasa vasorum were not unusual.

No trace of thyroid tissue was discovered in sections from the tissues of the neck. The pleural cavities were obliterated by fibrous adhesions. The left kidney was 1.5 times the size of the right, which was about normal in size. The capsules were slightly adherent. The surface showed numerous, deep scars as large as 1 cm. in diameter and several millimeters in depth. On section, the cortex was slightly diminished in thickness. The markings were indistinct, and there were numerous, tiny, red dots arranged in a radiate manner. The cortex in the region of the scars had been reduced to a narrow rim.

Microscopically, there was moderate thickening of the arterioles in the kidneys and other organs. Numerous glomeruli were fibrotic and hyalinized, but there was little interstitial fibrosis of the kidney. The glomeruli that remained were

extremely congested. The tubular cells showed marked granular degeneration. The larger vessels had undergone intimal thickening. In a few arteries the muscle cells of the media showed chromatrophic degeneration similar to that in the coronary arteries, pulmonary arteries, and aorta.

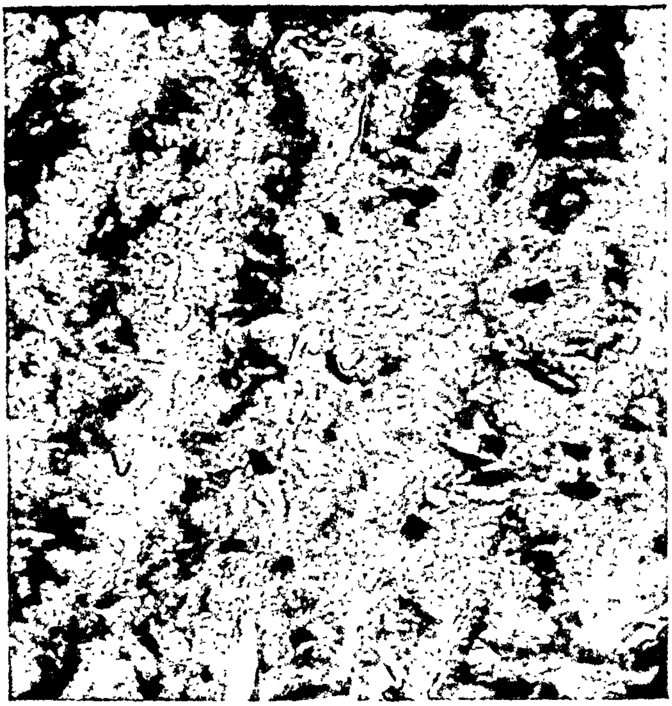

Fig. 3.—Photomicrograph (high power), showing the chromatrophic degeneration in the aortic wall. The white lines represent the degenerated material; the dark bands are muscle cells. The elastic tissue may be seen as small, sharp bands, with frayed ends. These broken ends indicate rupture of the fibers.

Fig. 4.—Photomicrograph (high power, special stain), showing the white degenerated material between the dark muscle bundles. The extremely large amounts of the degenerated material can be seen in this picture, as well as in many other areas of the aorta.

Sections of the hilar portions of the lungs showed extensive hemorrhage around the larger arteries. These vessels showed the same medial change as the coronary arteries and aorta. Throughout the lung, the alveolar walls were greatly thickened by an infiltration of histiocytes and fibroblasts. There were a few, small areas of organizing pneumonia.

The smaller vessels in the pancreas and in the capsule of the adrenal were moderately thickened.

DISCUSSION

It is thus seen that, in three cases of advanced and possibly malignant hypertension, complete removal of the thyroid gland was followed, in two instances at intervals of five months, and in a third instance at an interval of thirty-one months, by spontaneous rupture of the aorta. It may be significant that the third case, in which the rupture was delayed, was the only one of the three in which the patient received desiccated thyroid for a long time. It is, of course, possible that the thyroidectomy and chromatrophic degeneration in these three cases may have been a coincidence. This, however, seems improbable. It would seem more likely that the hypothyroidism and hypertension combined to produce the chromatrophic degeneration. Since spontaneous rupture of the aorta is a relatively rare occurrence, it seems improbable that this sequence of events could have been mere coincidence.

It is evident that in none of the cases were there clinical or pathologic manifestations of syphilis. No considerable atheromatous change in the aorta was apparent in the first case. In the second, there were a few, small, yellow streaks of fatty material in the ascending aorta, but none in the immediate vicinity of the laceration. The aorta of the third patient showed a few atheromatous plaques in the intima, and near the orifice of the right coronary artery there were small, elevated, atheromatous plaques in the intima adjacent to the lesions. As has been noted, none of these plaques was the seat of calcification or ulceration. It seemed improbable that they were etiologically significant in the production of the laceration. In all of the cases there was evidence of idiopathic cystic necrosis, variable in degree, of the aortic media.

The true cause of the chromatrophic degeneration of the media of the aorta is not known.[7, 9, 10] Its occurrence in three patients with hypertension who had had thyroidectomies suggests that there might be a relationship between the glandular activity and the disease of the blood vessels. Just how or what the mechanism is one cannot say. One possibly related fact is that the hearts of rabbits which have had their thyroid glands completely removed tend to accumulate mucoid substance between the muscle fibers.[11] This did not occur in human hearts. It is possible, however, that in hypertension, with strain on the aortic wall, the metabolism of the muscle of the aorta may be

greatly increased, and, therefore, that the induction of hypothyroidism, which causes an abnormality of metabolism, may bring about the deposition of abnormal products, as in myxedema.

It is true that autopsies in cases of myxedema have been notoriously few, and that, for many years, there have been almost none on patients who had not had thyroid treatment. Although our review of the literature is not complete, we have encountered no record of a case of myxedema in which aortic rupture occurred. That such accidents are infrequent must be evident. Whether the necrotic lesions of Erdheim[7] are consequent to hypothyroidism cannot be stated. Certainly the aortas of such patients have seldom been studied with the care necessary to demonstrate these somewhat subtle changes. It may be significant that relatively few patients with myxedema have excessively high arterial pressure. In the early stages of the disease the tendency to hypotension is well recognized. In long-standing hypothyroidism the elevation of blood pressure is not often great, and yields readily in most instances to treatment with desiccated thyroid.

It is our impression that complete removal of the thyroid in these cases contributed to, if it did not actually cause, a mucoid or necrotic lesion in the medial coat of the ascending aorta which so weakened the wall of that vessel that it was unable to withstand the excessively high blood pressure.

The presence of chromatrophic degeneration in the aortas of elderly persons suggests a relationship to arteriosclerosis[9] (Hempelmann). This relationship could not be definitely established in our younger group of subjects. There was some increase in the amount of calcium, but nothing more. The fact that our patients were young tended to rule out a nonspecific arterial degeneration as a cause of the disease. If one assumes a relationship between hypothyroidism and this disease, the fact that there was degenerative material in the walls of the smaller arteries emphasizes the possible importance of considering glandular dysfunction as an etiologic factor in many forms of arterial weakness and disease.

SUMMARY

In three cases of severe hypertension, in which total thyroidectomy had been done, death occurred as a result of rupture of the aorta. Although no notable change in the blood pressure occurred, the patients felt better, as a rule, immediately following the operation. In each case, varying degrees of chronic, idiopathic, aortic and arterial degeneration were found. It is suggested that this degeneration may result from a metabolic deficiency of aortic muscle under strain. It is suggested that there should be closer observation in such cases, in order to ascertain whether or not there is a relationship between disease of the glands of internal secretion and aortic and arterial disease. It is, of course,

recognized that the induced hypothyroidism and aortic cystic degeneration might have been merely coincidental.

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OBSERVATIONS ON THE CARDIOVASCULAR SYSTEM IN MYASTHENIA GRAVIS

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THE first description of myasthenia gravis was given by Thomas Willis in his "De Anima Brutorum,"[1] published in 1672. Accurate clinical descriptions of the syndrome appeared towards the close of the last century (Erb,[2] Goldflam,[3] and Jolly[4]). Studies on the subject in recent years have been made by Boothby,[5] and Kennedy and Moersch.[6]

The disease is characterized by rapid fatigue of voluntary muscles and may affect only localized groups of small muscles, e.g., the extra-ocular group and those used for chewing and swallowing, or it may seem to affect all groups of muscles in the body to an equal degree. Spontaneous remissions usually occur in about 25 per cent of the cases. The affection is not rare; Boothby has data on some 100 cases, and Viets and Schwab[7] recently reported therapeutic results in fifty cases in their special clinic.

In spite of numerous clinical reports and investigations, there is as yet no exact knowledge as to the nature of the disturbance in muscular contraction. From the work of Dale, Cannon, and others it is known that acetylcholine is liberated at the myoneural junction when muscular action takes place. This substance in some way "chemically mediates" muscular contraction. Excess acetylcholine is removed at once by an esterase (cholinesterase). In normal persons an equilibrium is maintained; in patients with myasthenia gravis this balance is disturbed.

No complete clinical studies or descriptions of cardiovascular abnormalities in myasthenia gravis are to be found in the literature, and there has been no note in any case report of any cardiac dysfunction which could be attributed to the disease. Lange[8] took roentgenkymograms in one case and felt that they were abnormal, i.e., that there were some aberrations in the contractions. Post-mortem studies on the hearts of patients with myasthenia gravis have usually shown nothing abnormal, although lymphocytic infiltration and muscle fragmentation have been reported by some.[9]

From the Cardiac Laboratory, and Paper No. 7 from the Myasthenia Gravis Clinic, Massachusetts General Hospital, Boston.

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For these reasons, and because the cardiocirculatory system is a delicate neuromuscular mechanism, it was thought worth while to search for abnormalities of the cardiovascular system in a group of myasthenic patients.

Careful interrogatory and physical examinations were carried out in fourteen cases of proved myasthenia gravis. Orthodiagrams were taken in every case. Venous pressure was measured according to the method of Burwell, et al.[10] Circulation rates were estimated with ether and lobeline, or saccharin. Electrocardiograms were taken with the patients recumbent and at rest, during carotid sinus pressure, and during the injection and period of action of mecholyl (10 to 15 mg.) and of atropine (gr. 1/50). The patients who were under treatment with prostigmine bromide by mouth omitted their medication overnight, and reported at the laboratory at 8:30 in the morning, without breakfast. In advanced cases the treatment was omitted for a shorter time, but in all of the cases the examination and test were performed only when all of the symptoms of myasthenia had appeared.*

CASE REPORTS

CASE 1.—E. T., a woman, aged 19, first came to the myasthenia gravis clinic in March, 1934, with ptosis of the lids of both eyes of two months' duration and some general weakness and fatigue. Since 1937 she had been taking prostigmine (45 to 60 mg. daily) and guanidine, with excellent results.

She had no cardiac symptoms. Orthodiagraphically, her heart was normal in size. Physical examination of the heart showed nothing except a functional, pulmonary, systolic murmur. The arterial pressure was 120/80, the venous pressure, 8 cm. of water. The saccharin time was 10 sec.; the ether time, 5 sec. The electrocardiogram showed normal rhythm, a rate of 85, a P-R of 0.16 sec., a slightly prominent P_2, and late inversion T_3 (normal record).

CASE 2.—C. Z., a woman, aged 26, was referred to this hospital in October, 1938, with a story of difficulty in talking and swallowing and weakness of the facial muscles, of six months' duration; there was very little general weakness. The patient responded only partially to prostigmine.

She had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed that the size of the heart was normal. The arterial pressure was 100/60; the venous pressure, 6 cm. of water. The saccharin time was 19 sec.; the ether time, 8 sec. The electrocardiogram showed normal rhythm with sinus arrhythmia, a rate of 65 to 75, a P-R of 0.16, a normal QRS, and upright T waves (normal electrocardiogram).

CASE 3.—J. P., a man of 54, came to the myasthenia gravis clinic in February, 1937, with ptosis of the lids of both eyes which had begun rather suddenly four months before. There was no general weakness. He responded immediately to prostigmine (90 to 120 mg. daily), and, as time went on, needed less and less of the drug; finally, in December, 1938, he was able to give up prostigmine treatment entirely, without any return of his symptoms. He has remained in this complete remission ever since.

He had no cardiac symptoms. Examination, during the remission, showed no cardiac abnormality. The orthodiagram showed no cardiac enlargement. The arterial pressure was 130/85; the venous pressure, 13 cm. of water. The saccharin time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal

*The authors are indebted to Dr. Paul D. White and Dr. Henry R. Viets for valuable criticism during the course of this investigation.

rhythm, a rate of 70, slight left axis deviation, a P-R of 0.15 sec., normal T waves, and a normal Lead IV (normal record).

CASE 4.—F. L., a woman of 46, came to the hospital in November, 1938, with a five months' story of fatigability, ptosis of the lids of both eyes, general weakness, and difficulty in chewing and talking. She was given prostigmine (60 to 75 mg. daily) and 2.125 Gm. of guanidine hydrochloride, with good results.

She had been breathless on undue exertion since the age of 21 and had occasional dyspnea at night; these symptoms were associated with her general weakness. In one attack she felt that her heart was stopping; occasionally she had nocturnal palpitation. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 130/85, the venous pressure, 11 cm. of water. The lobeline time was 7 sec.; the ether time, 4½ sec. The electrocardiogram showed normal rhythm, a rate of 78, a P-R of 0.15 sec., upright T waves, and slight right axis deviation (normal record).

CASE 5.—S. V., a woman of 19, came to the hospital in October, 1937, at the age of 17, complaining of difficulty in speaking and swallowing, weakness, and fatigue, of one and one-half years' duration. She has taken as much as 400 mg. of prostigmine daily since 1937, with definite improvement.

When excessively tired, she has had dyspnea in association with her general weakness. She has also been waked up at night, occasionally, when she has not taken her medicine. On examination, her heart was normal. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/70; the venous pressure, 9 cm. of water. The saccharin time was 14 sec.; the ether time, 6 sec. The electrocardiogram showed normal rhythm, a rate of 95, a P-R of 0.15 sec., and upright T waves (normal electrocardiogram).

CASE 6.—H. C., a man of 45, first came to the hospital in October, 1937, complaining of weakness of his hands, double vision, and some difficulty in chewing and swallowing, of two years' duration. He is now taking 75 to 90 mg. of prostigmine daily, with good results.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/70; the venous pressure, 10 cm. of water. The lobeline time was 13 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.16 sec., and slight elevation of R-T in Leads I and II (normal record).

CASE 7.—M. K., a 19-year-old woman, came to the hospital in March, 1935, because of five months of difficulty in speaking and swallowing. She has taken, since 1937, 120 to 160 mg. of prostigmine daily, with excellent results.

She had no cardiac symptoms or signs. The orthodiagram showed that the heart was not enlarged. The arterial pressure was 120/80; the venous pressure, 12.5 cm. of water. The lobeline time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.16 sec., a normal QRS, upright P waves, and slight right axis deviation (normal record).

CASE 8.—J. B., a 22-year-old man, came to the hospital in 1932 with a complaint of general weakness, particularly in his legs and arms. During the last three years he has been taking prostigmine (250 to 300 mg. daily), with the result that his symptoms have disappeared.

He had palpitation shortly after the onset of his myasthenia and tachycardia with the least excitement, but he has no cardiac symptoms now. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/80; the venous pressure, 14 cm. of water. The lobeline time was 27 sec.; the saccharin time, 25 sec.; and the ether time, 15 sec. The

electrocardiogram showed sinus arrhythmia, a rate of 80 to 60, a P-R of 0.14 sec., normal P waves, upright T waves, and normal QRS complexes (normal record).

CASE 9.—J. H., a man of 56, came to this hospital in June, 1939, with a story of palpebral ptosis of four months' duration, and marked difficulty in swallowing, talking, and chewing of three weeks' duration. He was given prostigmine (150 mg. daily), with marked improvement in his general condition.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 140/90; the venous pressure, 10.5 cm. of water. The lobeline time was 18 sec.; the ether time, 8 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright T waves in Lead II, and slight left axis deviation (normal record).

CASE 10.—C. L., a 24-year-old man, entered the hospital in July, 1939, with a complaint of general weakness, fatigue in chewing and swallowing, and transient diplopia of eighteen months' duration. He was given prostigmine (120 to 135 mg. daily), with alleviation of his symptoms.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no enlargement of the heart. The arterial pressure was 120/80; the venous pressure, 10 cm. of water. The lobeline time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal rhythm, a rate of 72, a P-R of 0.14 sec., normal QRS complexes, and upright T waves in all leads (normal record).

CASE 11.—S. S., a woman of 49, came to the hospital in 1937, complaining of general weakness and ptosis of the lids of both eyes which began in 1933. Since 1937 she has been taking prostigmine (120 mg. daily), with general improvement. She had rheumatic fever in childhood, as a result of which she was kept in bed for some time. She is an extremely neurotic patient, with severe osteoarthritis of one hip.

She had had no definite cardiac symptoms, but there had been signs and symptoms of bronchitis during the preceding few weeks. Examination of the heart was negative. The orthodiagram showed no enlargement of the heart. The arterial pressure was 140/100; the venous pressure, 17 cm. of water. The saccharin time was 19 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright T waves in all leads, and no abnormal axis deviation (normal record).

CASE 12.—E. H., a 27-year-old woman, came to this hospital in March, 1932, with a story of difficulty in speaking and swallowing, and bilateral palpebral ptosis which began gradually five months previously. She was given prostigmine (120 to 160 mg. daily) in January, 1937, with marked improvement in her symptoms.

She had had occasional attacks in which she felt that she was unable to breathe and was going to die, but these occurred only when she was without medicine. Examination of the heart was negative. The orthodiagram showed that the size of the heart was normal. The arterial pressure was 125/80; the venous pressure, 9 cm. of water. The saccharin time was 13 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright R waves in Leads I and II and T waves in Lead II, inversion of all waves in Lead III, and slight left axis deviation (normal electrocardiogram).

CASE 13.—W. D., a man, 66 years of age, was referred to this hospital in November, 1938, because of ptosis of the lids of both eyes, double vision, general weakness, and difficulty in chewing, swallowing, and talking of six months' duration. He was given prostigmine by mouth (150 mg. daily), and is doing well.

He had no cardiac symptoms, but was known to have had hypertension for a few years. Examination showed that he was apparently a healthy man, with no enlargement of the heart. The heart sounds were not remarkable; the aortic second sound was louder than the pulmonic second. The blood pressure was 166/96. The electrocardiogram was normal; it showed normal rhythm, a rate of 75, notched P waves in Leads I and II, and a flat T_3.

CASE 14.—S. S., a 64-year-old woman, came to the myasthenia gravis clinic in May, 1937, with intermittent palpebral ptosis of almost nine years' duration. She was given prostigmine (90 to 120 mg. daily) and is somewhat improved.

She has had breathlessness, when working and walking, for two years, but she has had no nocturnal dyspnea and is able to sleep without extra pillows. She is known to have had hypertension for ten years. Examination showed a palpable thyroid gland, but no definite signs of hyperthyroidism. Fluoroscopic examination showed enlargement of the heart, especially of the left ventricle. The heart sounds were normal, and the blood pressure was 185/105. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.14 sec., notching of QRS in Lead III, and a variable T_3 (normal record).

SUMMARY OF CARDIAC EXAMINATIONS

Examination of the heart has shown no abnormalities in this group of fourteen patients with myasthenia gravis. Some patients, as in Cases 4, 5, and 11, have had some difficulty in breathing when they are not taking prostigmine. Others, as in Case 4 and Case 8, have had occasional attacks of palpitation. Inasmuch as we carried out our examinations when the patients were not being treated, and could then find no abnormalities, we believe that there is no justification for attributing these symptoms to any disturbance in the myocardial function; they are more likely the result of the general weakness and nervousness engendered by the disease.

In Case 11, the patient had a rather high venous pressure and a slightly elevated diastolic arterial pressure when she was first examined. We think that the bronchitis which was present was sufficient to account for these slight abnormalities. When she was examined two months later, she appeared well.

In Case 12, the patient complained of occasional attacks of dyspnea, one of which we had the opportunity to observe. Following the measurement of the circulation time, she developed marked bradycardia and a drop in the blood pressure, accompanied by dizziness. The attack was quickly relieved by adrenalin. Similar attacks were produced by carotid sinus compression, proving that there was an increase of vagal activity; this was evidence against the possibility of any myasthenic involvement of the heart.

In Cases 13 and 14 there was slight elevation of the arterial blood pressure; this had been known for many years. There had been no apparent change with the onset of myasthenia gravis. This fact also suggests that the heart is not involved in this disease.

EFFECT OF VAGUS STIMULATION IN PATIENTS WITH MYASTHENIA GRAVIS

Inasmuch as myasthenia gravis has been thought to be caused by dysfunction of the action of acetylcholine at the myoneural junction, it was of interest to ascertain whether the vagus nerve was exerting its normal control on the heart. Therefore, we tested the effect of carotid sinus pressure, mecholyl, and atropine on all fourteen patients. The results are given in Table I.

Carotid Sinus Pressure.—The carotid sinus reflex was tested in all fourteen patients, and was active in ten. The decrease in the heart rate varied from fifteen to twenty-five beats per minute. In three other patients there was extreme slowing, i.e., to thirty-five or forty beats per minute, and, in the remaining patient (Case 12), complete S-A block was produced momentarily.

Mecholyl.—The effects of mecholyl were studied in ten patients. Nine patients were under treatment with prostigmine, a drug which is synergistic with mecholyl, although at the time of the test the drug had been withdrawn long enough to allow the development of myasthenic symptoms. For these reasons, only small doses of mecholyl were administered, namely, 10 to 15 mg. The drug was injected subcutaneously under basal conditions; electrocardiograms and blood pressures had been recorded previously. Immediately after the injection the electrocardiogram was recorded continuously, the blood pressure was taken, and any symptoms were noted. Because of their difficulty in swallowing, the salivation produced by mecholyl caused some patients much discomfort. In all cases a marked tachycardia and fall of blood pressure were noted. The tachycardia started about thirty seconds after the injection, attained its maximum after three minutes, on the average, and remained at a constant rate for approximately ten minutes. The maximum fall in blood pressure also occurred within about thirty seconds; the pressure then gradually returned to normal, before the heart rate. Even when the decrease in blood pressure preceded the tachycardia, there was no direct relationship between them.

In four cases, the electrocardiograms showed, in addition to the sinus tachycardia, slight prolongation of the P-R interval (from 0.02 to 0.04 second). There were only a slight depression of the S-T segment in three cases and slight or definite flattening of the T waves in four cases. These changes in the ventricular complexes were closely related to the tachycardia in all cases. In addition to the cardiovascular symptoms, the patients had marked sweating, which developed within five minutes, and profuse salivation; some had nausea, and one had vomiting. In five cases an injection of 1.5 mg. of atropine was necessary in order to stop the mecholyl symptoms. These cases were those in which prostigmine had been omitted only a comparatively short time before.

The signs and symptoms produced by mecholyl in this group of patients were essentially similar to those which occur in normal subjects.

TABLE I

RESULTS OF TESTS WITH MECHOLYL AND ATROPINE

CASE NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SEX	F	F	M	F	F	M	F	M	M	M	F	F	M	F
AGE	19	26	54	46	19	42	19	22	56	24	49	32	66	64
Daily Dose of Prostigmine in mg.	60	100	0	75	400	90	160	300	150	120	120	160	150	120
Hours Since Last Medication	8	8		10	10	10	4	8	8	15	5	12	4	8
Resting Pulse Rate	85	75	80	80	80	70	80	80	75	75	75	75	75	80
Blood Pressure	120/80	100/60	130/85	130/85	105/75	105/70	120/80	105/80	140/90	120/80	140/100	125/80	166/96	185/105
Mecholyl (mg.)	10	10	15	10	10	10	10	10	10	10				
Drop in B.P. (mm. Hg)	30	5	10		15	9	60	15	15	18				
Time to fall (sec.)	30	30	120	45	60	45		45	60	30				
Time to return to normal (min.)	17	2	5	8		6		9	6	20				
Maximum tachycardia	160	150	100	140	150	100	140	135	120	140				
Time to attain maximum (min.)	6	2	3	8	1.75	2	3	8	3	5				
Time of onset of tachycardia (sec.)	15	30	60	60		0	30	30	60	30				
Atropine (gr.)	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50		1/50
Maximum tachycardia	160	120	90	125	125					120	120	140		125
Time to attain maximum (min.)	16	20	10	15	20					15	15	20		15
Atropine for severe reactions		Yes			Yes		Yes	Yes	Yes					

Any difference that was noted was regarded as a result of the nervous reactions following the discomfort caused in these myasthenic patients. The marked response in the four cases in which prostigmine medication had been omitted for only a few hours may have been caused, in part, by summation of the two drugs. As Dameshek, et al.,[11] have shown, when small doses of mecholyl are given after the administration of prostigmine, a marked effect is produced. The fact that these patients were not taking prostigmine at the time of the test is no proof that all of the drug had been eliminated.

It is not the purpose of this paper to discuss the tachycardia that normally follows the injection of mecholyl, but, judging from the results which were obtained, we believe, as Dameshek does, that the fall in blood pressure is not the only factor in the production of the tachycardia.

Atropine.—The effect of atropine was studied on nine patients. One-fiftieth grain was given subcutaneously in every case, at a time when the patients were not taking prostigmine. As in the case of mecholyl, the electrocardiogram and blood pressure were recorded. In all of the cases tachycardia appeared approximately three minutes after the administration of atropine and reached a maximum after fifteen minutes. No definite alteration in blood pressure accompanied the changes in heart rate. The electrocardiogram showed, in addition to the sinus tachycardia, slight shortening (0.02 second) of the P-R interval in six of the eight patients. Only a slight depression of the S-T segment occurred in two cases, and slight flattening of the T waves in two other cases. The reactions to atropine, as well as to mecholyl, of patients with myasthenia gravis are the same as those of normal subjects.

POST-MORTEM EXAMINATION OF PATIENTS WITH MYASTHENIA GRAVIS

Post-mortem examination in cases of myasthenia gravis has been reported as showing lymphocytic infiltration in all muscles, but, in general, the heart has been considered normal. Barton and Branch[9] found marked lymphocytic infiltration in one case in which there had been marked myasthenia gravis symptoms and a high basal metabolic rate.

We had the opportunity of performing a post-mortem examination in one of our cases (Case 2); the patient died from bronchopneumonia and massive collapse of the lung. Histologic and gross examination of the heart showed nothing abnormal. In addition, re-examination of the hearts of two patients with myasthenia gravis who had died previously at the Massachusetts General Hospital disclosed no abnormalities.

CONCLUSIONS

1. The cardiovascular systems of fourteen patients with myasthenia gravis of varying duration and severity were studied.

2. Clinical examination of the cardiovascular system was negative in all cases.

3. The carotid sinus reflex was active in every case.

4. The reaction to the subcutaneous injection of 10 to 15 mg. of mecholyl was the same as that which occurs in normal subjects.

5. The reaction to the administration of $\frac{1}{50}$ grain of atropine was also normal.

6. Post-mortem gross and histologic study of one of these patients, as well as of two others at the Massachusetts General Hospital, showed no cardiac abnormality.

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THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF QUINIDINE SULFATE ON THE DEVELOPMENT OF VENTRICULAR FIBRILLATION FOLLOWING SUDDEN OCCLUSION OF THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY

AN EXPERIMENTAL STUDY

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SUDDEN occlusion of an important branch of a coronary artery results in a characteristic sequence of events which may terminate in fatal ventricular fibrillation.

There is a remarkable similarity between the symptoms exhibited by an animal dying of ventricular fibrillation and those of a man dying suddenly of coronary occlusion; in both cases, there are cyanosis, pallor, venous congestion, gasping respirations, loss of pulse pressure, and a sudden loss of consciousness, followed by death.

In the majority of cases in which death occurs suddenly as a result of ventricular fibrillation, autopsy reveals a coronary lesion, usually in the form of sclerosis. That the presence of coronary sclerosis triples the incidence of sudden death from coronary thrombosis has been shown by Levy's[1] study of a large group of cases. There is also a relationship between sclerosis of the coronary arteries and ventricular fibrillation, for in the majority of cases in which death occurs suddenly as a result of ventricular fibrillation autopsy reveals such lesions.

At the present time the number of cases in which the mechanism of the dying heart has been recorded by the electrocardiograph is relatively small. Similar records in cases of "sudden" death are quite rare. However, in the majority of these cases death was caused by ventricular fibrillation. Although one or two instances of survival have been recorded, most patients die suddenly once true ventricular fibrillation becomes established.

Several theories which have been advanced as to the cause of sudden cardiac death will be discussed in detail in a subsequent paper. At this time only experimental ventricular fibrillation will be considered. As early as 1850, Hoffa and Ludwig[2] recognized ventricular fibrillation, produced by electrical stimulation, as a cause of death in animals. Death produced in animals by chemical, mechanical, and various other means is also, in most cases, the result of ventricular fibrillation. Some-

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what more comparable to the clinical condition which leads to ventricular fibrillation and sudden death is the experimental occlusion of a major branch of a coronary artery in the conscious animal.

Many drugs, with entirely different properties, have been employed in the past in the treatment of cardiac irregularities. One of these drugs, quinidine sulfate, has been used widely as a preventive of auricular and ventricular tachycardia, as well as in the treatment of these ectopic rhythms once they become established. Its use has also been advocated for the treatment of auricular fibrillation. Hepburn and Rykert[3] reported twenty-six cases of ventricular tachycardia, in nine of which quinidine sulfate was given intravenously. They concluded "that intravenous quinidine sulfate may be a life-saving drug in ventricular tachycardia." Morawitz and Hochrein[4] regarded quinidine sulfate as a highly successful prophylactic in the treatment of patients who were liable to sudden cardiac death from ventricular fibrillation, and Stepp and Parade[5] advocated its use as a means of preventing fibrillation.

Quinidine sulfate abolishes vagal tone, thus lengthening the refractory period of auricular muscle and decreasing the transmission rate of the nervous impulse. It also acts directly on the ventricular and auricular myocardium, lengthening the refractory period and slowing the rate of conduction. Furthermore, it decreases conduction time in the junctional tissue.

That these actions are not always specific has been shown by the fact that cases of auriculoventricular block, extrasystoles, paroxysmal tachycardia, and even fatal ventricular fibrillation have been reported as a result of using large doses of this drug in the treatment of heart disease. It has been suggested that the development of ventricular fibrillation is caused by the establishment of circus movements in the ventricle, and that the latter result from a greater reduction in the rate of conduction in the ventricular myocardium than lengthening of the refractory period.

Since quinidine sulfate is an important drug clinically, it was thought advisable to study its effects on the development of the ventricular tachycardia and ventricular fibrillation which are produced experimentally by coronary artery ligation in conscious animals. The purpose of this paper is to present the results of such a study.

EXPERIMENTAL PROCEDURE

Normal, healthy dogs which weighed approximately 6.5 kg. were used. Electrocardiograms were taken before operation, before and after drug administration, and at various intervals following ligation.

The heart was exposed through the left fourth intercostal space. After careful dissection of the circumflex branch of the left coronary artery, a loose ligature was placed around the vessel in the manner previously described.[6] Sufficient ligature was left in the chest to allow for lung expansion without causing tension

on the loosely tied knot, and the loose ends were led from the chest via the wound. The chest was then closed as tightly as possible, and a sterile collodium dressing applied.

In all cases, intratracheal ether anesthesia was given following the subcutaneous administration of one-quarter grain of morphine sulfate.

When the animal had completely recovered from the effects of the anesthetic, i.e., in approximately twenty-four hours, it was carefully carried from its cage, in order to avoid unnecessary excitement, and a second electrocardiogram taken. Quinidine sulfate, in relatively large doses (32.5 mg./kilo.), was then given slowly by intravenous injection. Further electrocardiograms were taken.

The effects of the drug were not uniform. Distress was evidenced by muscular twitching, which was usually followed by a severe convulsion. The convulsion was accompanied by marked dyspnea, cyanosis of oral mucous membranes, salivation, and, frequently, by vomiting. Most of these symptoms could be avoided if the drug was given very slowly, but in some animals the rate of injection or the amount given was apparently not related in any way to the resultant distress.

Ten minutes after the administration of the drug, coronary occlusion was produced by traction on the extrathoracic ends of the ligature. Very little, if any, pain was experienced by the animal when the artery was ligated.

The various electrocardiographic changes which occurred were then recorded (Lead II) until the animal either died or acted as if it would survive. In these latter cases, electrocardiograms were taken at various intervals for several days.

Twenty animals were used in this series. Of this number, eleven, or 55 per cent, died within twenty-four hours. Nine of these eleven animals died, however, within five minutes of the ligation.

ELECTROCARDIOGRAPHIC CHANGES

In all cases, the quinidine sulfate produced a definite acceleration of the heart rate (Fig. 1 *B*). In a few instances, however, isolated extrasystoles were also observed. Within two or three seconds of ligation many extrasystoles appeared, and, within ten seconds, the normal ventricular complexes had been replaced by long runs of ventricular extrasystoles. Almost immediately, ventricular tachycardia became well established.

In the animals which eventually recovered, the stage of ventricular tachycardia was usually maintained for some time (Fig. 1 *F*). After this stage, the ventricular complexes became quite irregular in shape, rate, and amplitude. There followed a progressive decrease in the amplitude of the ventricular complex, together with better definition of the R-T segment (Fig. 1 *H*). At the same time, the beating became progressively more regular, until, after about thirty minutes (Fig. 1 *I*), both the auricular and ventricular complexes were approximating the normal. The axis deviation which is typically associated with occlusion of the circumflex branch of the left coronary artery developed within the next few days.[6] Within eighteen to twenty-four days the electrocardiogram was essentially normal (Fig. 1 *J*).

The electrocardiograms of the animals which did not survive likewise showed a rapid elevation of the R-T segment, a high take-off of the T wave, a marked increase in the amplitude of the waves, and an early

absence of P waves (Fig. 2). Usually, the rate was considerably accelerated. The early ventricular tachycardia was soon folowed by a more rapid type, with waves of great amplitude (Fig. 2 *D*), which rapidly passed into the stage of true ventricular fibrillation (Fig. 2 *E*). Fatal ventricular fibrillation in these cases almost always developed within ninety seconds of ligation.

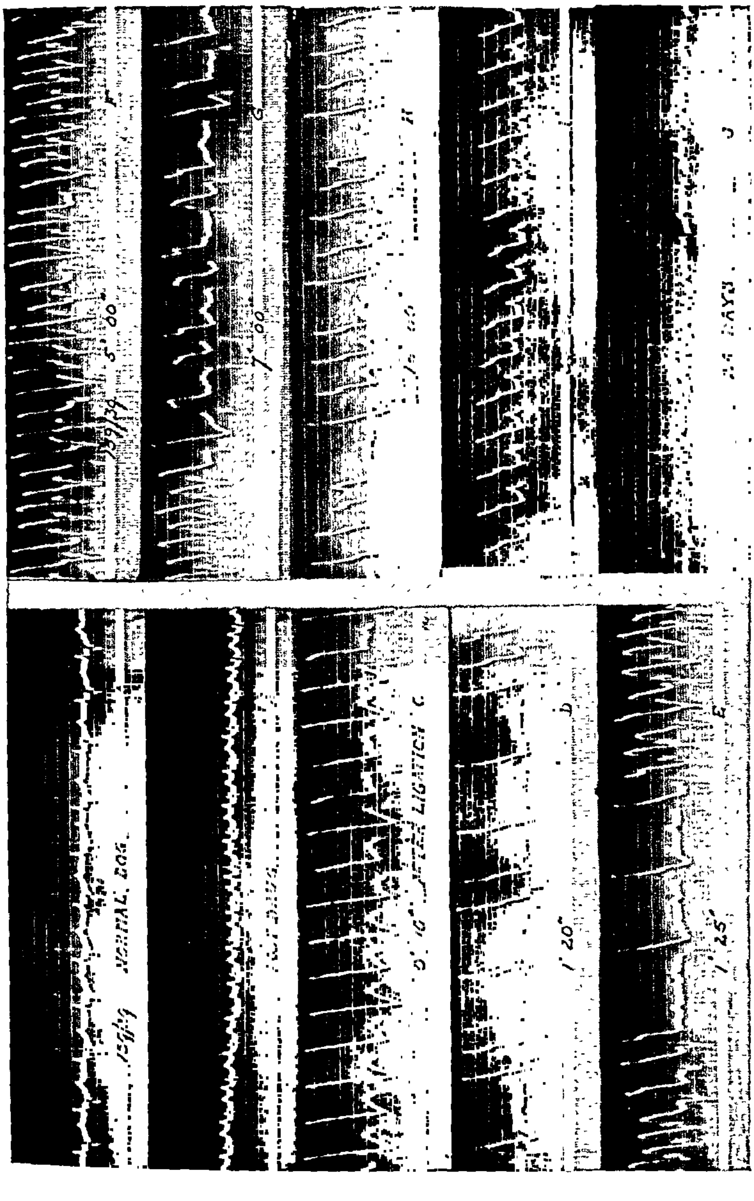

Fig. 1.—Lead II, showing progressive changes following ligation of the circumflex branch of the left coronary artery of a dog treated with quinidine sulfate. Note early onset of gross cardiac irregularities and immediate rise of the R-T segment.

COMMENTS

In these experiments quinidine sulfate was used in relatively large doses so that a maximal effect could be observed. This dose, however, was not grossly out of proportion to that which has been used clinically.[3]

The effect of intravenously injected quinidine sulfate is to quicken the heart rate; this acceleration may or may not be associated with occasional ventricular extrasystoles.

There are significant differences between the electrocardiograms of an animal which has been previously treated with quinidine sulfate, and a normal, untreated animal, following ligation of the circumflex branch of the left coronary artery. The sequence of events in the latter is a progressive rise in the R-T segment, extrasystoles, and ventricular tachycardia, which in most cases is followed by ventricular fibrillation (Fig. 3). When ventricular tachycardia becomes well established in animals which did not receive quinidine sulfate, it is practically always followed by fatal ventricular fibrillation. However, in an animal which has been treated with quinidine sulfate, ventricular tachycardia is apparently much more easily initiated and occurs more frequently, but the number of recoveries once the tachycardia becomes well established is much larger than in untreated animals.

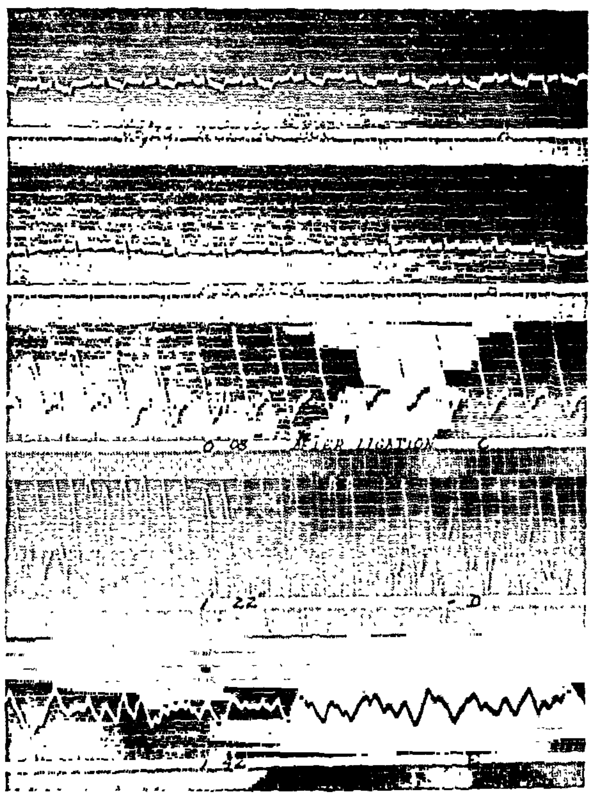

Fig. 2.—Lead II, showing changes preceding fatal ventricular fibrillation in a quinidine-treated animal. Note early cardiac irregularities, with rapid onset of ventricular tachycardia.

Examination of the electrocardiogams indicates that, after the intravenous injection of quinidine sulfate and subsequent coronary ligation, the myocardium is more sensitive to the establishment of ectopic foci, with the result that marked irregularities occur. Extrasystoles from many foci and ventricular tachycardia were frequently observed. Although recovery from these serious disturbances in the cardiac mechanism was more frequent than in untreated animals, and the mortality was lowered somewhat (from about 75 per cent to 55 per cent), it would

appear that quinidine sulfate is of little use in the preventive treatment of disordered mechanisms caused by experimental occlusion of coronary arteries. Indeed, it hastens their onset.

However, quinidine sulfate does abolish almost completely the cardiac pain so characteristically experienced by conscious dogs after ligation of a main branch of a coronary artery. The afferent pain pathways from the heart thus appear to have been depressed by this drug. This suggests that pain pathways are separate from those which produce fibrillation reflexly.

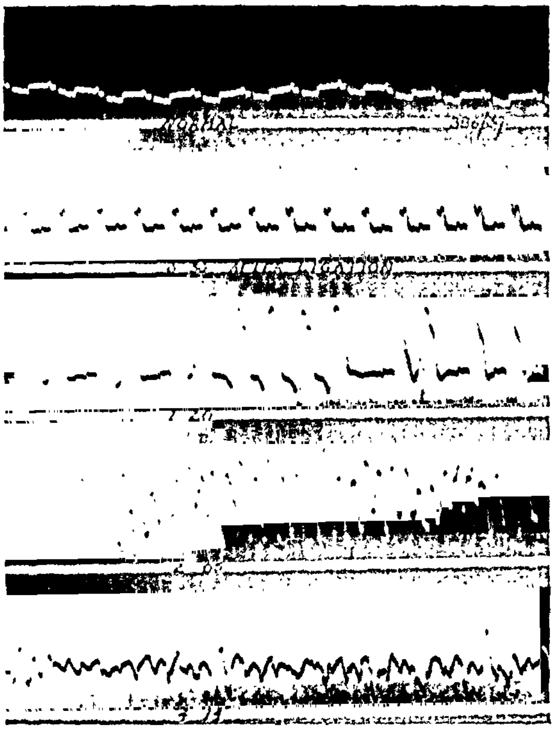

Fig. 3.—Lead II, showing progressive changes preceding fatal ventricular fibrillation in a normal, conscious dog, following ligation of the circumflex branch of the left coronary artery. Note gradual build-up of the R-T segment.

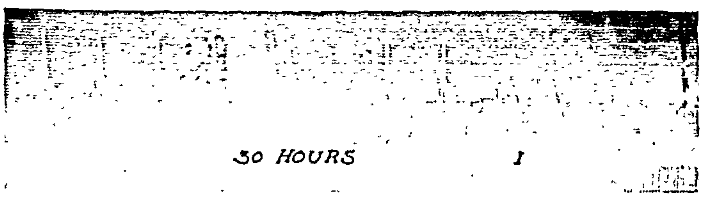

Fig. 4.—Lead II, showing sudden change of foci initiating extrasystoles from right to left ventricular myocardium.

The electrocardiograms also show that, although it was the circumflex branch of the left coronary artery that was ligated, the majority of the foci which initiated the extrasystoles and tachycardia were located in the right ventricle. However, in some instances there was a sudden shift of foci from the right ventricle to the left, as shown in Fig. 4. Also, the

form of the extrasystoles was not the same in every case, indicating that the foci which were initiating the irregularities must have been continually shifting their positions in the ventricular myocardium.

SUMMARY

1. Quinidine sulfate depresses the cardiosensory mechanism in dogs. This suggests that pain pathways are separate from those which produce fibrillation reflexly.

2. Quinidine sulfate renders the dog's myocardium more susceptible to the development of cardiac irregularities. Extrasystoles of left, as well as right, ventricular origin were recorded.

3. Quinidine sulfate lowers, to some extent, the mortality caused by coronary occlusion in dogs. In twenty animals the mortality was 55 per cent, as compared to 75 per cent in a control series.

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Department of Clinical Reports

LEFT AURICLE WITH A CAPACITY OF 1,695 GRAMS OF BLOOD IN A CASE OF MITRAL STENOSIS

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IN 1931, Bland, Balboni, and White[1] reported a case of "Enormous Increase of Heart Volume With Mitral Stenosis," and noted the paucity of volumetric data in such cases. They described a heart which weighed 4,600 grams when filled, with the pericardium attached, and 850 grams when emptied and stripped in the usual manner. The left auricle held 1,760 grams of fluid and the right auricle 660 grams; the latter was the largest figure on record. Only three other cases[2, 3, 4] were found in which the left auricular capacity was larger. Although numerous reports of massive enlargement of the left auricle have appeared since that time, I have found no case in which the capacity equalled that in those four or in the additional case herein reported.

CASE REPORT

E. P., a man, aged 28, was admitted to the medical service of the Miller Memorial Hospital on Sept. 18, 1939, with complaints of dyspnea, orthopnea, edema of the legs, ascites, and weakness. He had had heart trouble as long as he could remember; even in childhood his activities were limited. Two years earlier he had had his first attack of congestive heart failure. He improved after five weeks in bed, and quite comfortably engaged in light work until two months before admission, when he was forced by increasing shortness of breath to go to bed. General circulatory failure ensued, and death occurred Sept. 23, 1939.

In early childhood he had had chorea and occasional attacks of tonsillitis. There was no history of rheumatic fever or scarlet fever. There had been frequent nosebleeds during childhood and two during the preceding week. Swelling of the lower extremities below the knees had been present in varying degrees for many years.

Examination revealed a well-developed and fairly well-nourished white man who appeared to be about 25 years of age. He was alert, but conserved all possible energy by lying quietly. He breathed with considerable effort. The neck veins were markedly distended. The thorax was of the "pigeon breast" type, with a depth approximately equal to the width; the excursion was limited, and the breath sounds were obscured by roaring heart sounds. Complete dullness extended below the fourth intercostal space. The heart was completely irregular, and the rate was about 70 beats per minute. The apex impulse was diffuse, and extended low in the left anterior axillary line. There was a systolic retraction of the precordial intercostal spaces. A systolic roar and a less intense diastolic murmur were heard over the entire chest. The blood pressure was approximately 118/80.

The liver extended to the level of the umbilicus. It was pulsating, hard, and tender. Ascites, with shifting dullness in the flanks, was noted. There was considerable edema of the scrotum and extremities.

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Laboratory Data.—The urine contained albumin (three plus) and numerous hyaline casts. The hemoglobin was 13 grams, the erythrocyte count, 4,230,000, and the leucocyte count, 5,950, with a differential count of 62 per cent polymorphonuclears, 35 per cent lymphocytes, and 3 per cent large mononuclears. The blood Wassermann reaction was negative. An electrocardiogram showed auricular fibrillation, right

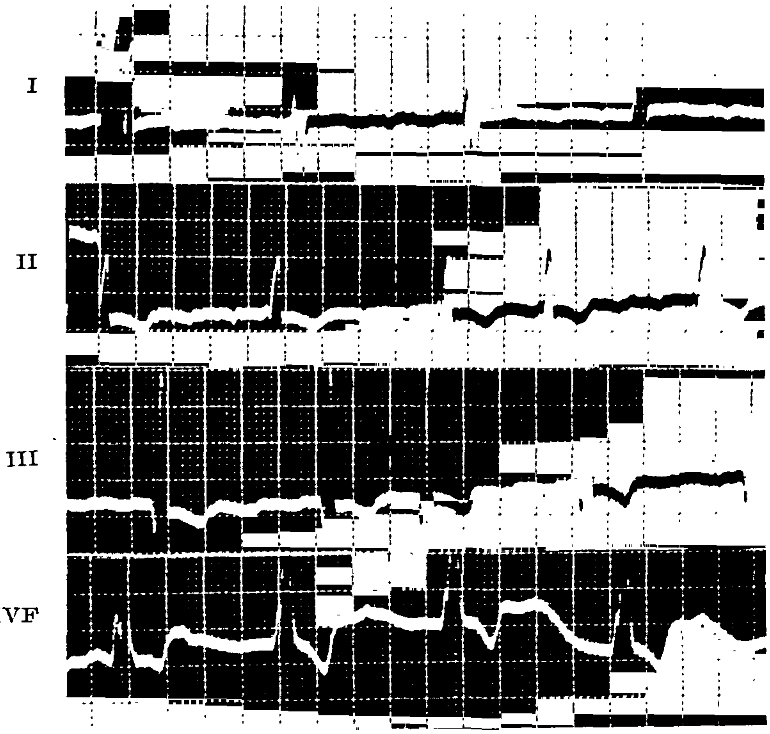

Fig. 1.—Electrocardiogram taken Sept. 18, 1939, five days before death. It shows auricular fibrillation, right axis deviation, low T_1 and inversion of T in II, III, and IVF. Lead IVF is international IVF.

Fig. 2.—This roentgenogram was taken at a 35-inch tube distance. It shows the enormous, smoothly rounded left auricle extending to the right chest wall. There was relatively little distortion of the size, shape, and position of the heart, as ascertained by clinical methods.

axis deviation, and abnormal S-T segments (Fig. 1). A roentgenogram of the chest (Fig. 2) showed a massive heart shadow and some congestion of both lungs.*

The patient's course during the short period of hospitalization was unsatisfactory. No benefit was obtained from digitalization and dehydration with salyrgan. Oxygen gave temporary relief, and, together with small doses of morphine, maintained an extraordinary degree of comfort. Death occurred at 5:15 A.M. on Sept. 23, 1939, and was not actually observed. A short time before, the floor nurse reported that the patient was sleeping quietly and breathing fairly easily.

The autopsy was performed by Dr. G. L. Berdez, clinical pathologist to St. Mary's Hospital, Duluth. Many details which are not pertinent will be omitted.

Fig. 3.—Anterior view of the excised heart and lungs immediately after removal. The lungs and the reflected pericardium lie at the upper portion. The ventricles are at the lower right, with left auricular appendage at the upper end of the interventricular sulcus. The left auricle occupies the large area to the left of the ventricles and basal vessels, and shows a surface which is partly muscular and mostly smooth and shiny.

The body was emaciated (grade II). There were innumerable petechiae in the skin, mainly over the shoulders, thighs, and chest. The chest was thicker than it was wide; the transverse diameter was 25½ cm., and the anteroposterior was 27 cm. There was edema below the knees. The peritoneal cavity contained 1,200 c.c. of slightly bloodtinged, straw-colored fluid. The liver extended 1½ cm. below the costal margin in the right midclavicular line. The left half of the diaphragm extended to the fifth intercostal space, and the right to the sixth. The left pleura showed ex-

*A sphygmogram taken on a Cameron Heartometer by Dr. C. M. Smith on July 5, 1939, was interpreted by him as showing a mitral stenosis type of bulging of the descending limb and a few ventricular extrasystoles.

tensive fibrous adhesions, and the right pleura showed a few fibrous adhesions between the lower lobe and the diaphragm, and contained about 40 c.c. of a dark, straw-colored fluid.

The heart occupied the entire lower half of the thoracic cavity; the relative extent of the individual chambers is shown in the photographs of the excised organs (Figs. 3 and 4). The left auricle extended to the right above the right auricle and over the right pulmonary veins. The heart and lungs were removed in toto, and the utmost caution was observed in tying off vessels in order to avoid leakage.* After removal, the specimen was immediately photographed, and then fixed in formalin solution for five days. This was done at the suggestion of Dr. Arthur H. Wells, clinical pathologist to St. Luke's Hospital, Duluth, who also prepared the specimen for display in accordance with his technique (soon to be described under the title of "The Preparation of Pathological Specimens" in the technical supplement of the *J. Am. Soc. Cl. Path.*). The volumetric measurements and gross examination of the fixed heart were made by Doctors Berdez and Wells and the author.

Fig. 4.—Posterior view, showing the massive, cystic appearance of the left auricle.

The weight of the heart filled, but stripped of pericardium, was 3,225 Gm.; the weight empty was 870 Gm.; the weight of the blood in the various cavities, removed separately, was as follows: left auricle, 1,695 Gm., right auricle, 405 Gm., left ventricle, 135 Gm., and right ventricle, 120 Gm. The measurements of the heart

*The care required to remove such a heart intact can be compared with the surgical removal of an ovarian cyst of similar size. Rupture would preclude accurate measurement of the blood content.

after removal, but before opening, were as follows: total length, 33 cm.; left auricle 22 cm. wide, 22 cm. in vertical diameter, and 15 cm. thick. The mitral cusps formed a slit 3.7 cm. long by 0.2 to 0.5 cm. wide. They were partly fused and calcified; the calcification formed a rectangular surrounding mass which was irregular, hard, and rigid, and measured about 2 by 6 cm. (Fig. 5). The tricuspid valve admitted four fingers. The pulmonic valve was normal, and the aortic valve was slightly thickened, but relatively sufficient. The coronary orifices were normal and the arteries themselves in good condition. The foramen ovale was closed; the myocardium was smooth and congested. Both lungs were diffusely congested, as were all of the parenchymatous organs. The adrenals showed but little lipoid, with a rather thick pigment layer and only a moderate amount of medullary substance. The liver showed marked central chronic passive congestion, some fatty change, and an increase in consistency but decrease of fragility. The aorta showed a few yellowish deposits in the intima. There was a middle dorsal kyphosis. Blood in the body cavities coagulated very rapidly.

Fig. 5.—Roentgenogram of the excised heart, showing the calcification about the mitral orifice. Before taking, the heart had been fixed and stuffed with cotton. The different densities of the thin left auricular wall and the other tissues are clearly shown. Calcification about heart valves is seldom visible in roentgenograms of living subjects except when they are taken with a special technique, although it is easily visualized under the fluoroscope in a large percentage of cases.

Microscopic examination of the tissues revealed nothing unusual. The lungs showed marked passive congestion, and the alveoli contained much coagulated albuminous material and numerous erythrocytes; some alveoli contained mononucle-

ated cells loaded with brownish pigment granules (heart failure cells). Some of the alveoli were larger than normal (emphysematous). The kidneys showed distended glomerular loops, and the tubules contained coagulated albuminous material and had a lining cytoplasm which was often slightly granular.

Pathologic Diagnoses:

1. Mitral stenosis and insufficiency, with calcification (grade IV).
2. Hypertrophy and dilatation of the heart.
3. Extreme dilatation of the left auricle.
4. Partial collapse of the lungs (caused by encroachment of the heart).
5. Chronic passive congestion of the lungs, with extensive pleural adhesions.
6. Central chronic passive congestion of the liver.
7. Beginning cardiac cirrhosis of the liver.
8. Ascites.
9. Edema of the legs (two plus).
10. Chronic passive congestion of the spleen.
11. Petechiae in the skin.
12. Terminal hemorrhages in the epicardium and the mucosa of the stomach and intestines.

DISCUSSION

This case is reported for several reasons:

1. The left auricular dilatation, substantiated by volumetric data, is one of the largest on record.

2. A roentgenogram of the chest, although it was not a teleoroentgenogram, helped to visualize the position of the heart in the chest.

3. An electrocardiogram which was taken a few days before death showed what one would expect with such clinical and pathologic findings.

4. The changes are particularly well illustrated by a roentgenogram of the excised organ, which shows the extent of the calcific process about the mitral valve.

The relation between the weight of contained blood and the capacity for water is speculative. Dr. Wells feels that the fixation employed in this case altered the blood weight very little, decreasing it if it changed it at all. It seems probable that more tension would result from filling the heart with water, and that the figure thus obtained would exceed the 1,695 Gm. blood weight.

Such a case impresses one with the remarkable adaptability of the cardiovascular mechanism. The accommodation to gradual changes leads one to speculate on the rationale of obtaining the optimum adaptation when other lesions are present. The pumping action of the enormous auricle was supplanted by an obviously small gravitational flow into the left ventricle, and, to a larger extent, by rhythmic pressure exerted by the diaphragm and accessory muscles of respiration; and, finally, the effectiveness of these was maintained only by the numerous factors which act to maintain vascular tone.

The author wishes to express his appreciation to Dr. Gage Clement and Miss Leve Bergholtz, of the St. Luke's Hospital X-ray Department, for the photographs and roentgenogram.

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LONG SURVIVAL FOLLOWING CORONARY THROMBOSIS

E. H. Drake, M.D.
Portland, Me.

Experience has taught us not to take an extremely pessimistic attitude regarding the outcome of coronary occlusion. Thirty years ago coronary thrombosis was a medical curiosity, known only to pathologists. After the belated recognition of Herrick's[1] observations, it was at first believed that hardly more than one-half of the patients survived the acute attack. Time has shown that this figure is far too high; we now believe that the immediate mortality of coronary thrombosis under the best conditions is about 15 per cent. The future of the survivors, however, is not as good as this. Statistics covering several large groups of patients show that the period of survival does not run much beyond two years.* If this be true, it would appear that our optimism must be confined, in the main, to the prognosis of the immediate attack. We might almost as well consider that such patients are permanently disabled and count it hardly worth while to attempt to return them to active life. The only ray of hope seems to be that a small percentage of survivors will make surprising recoveries and be able to live and work for a varying number of years. The attitude of the physician today, therefore, is that he must not be too depressed about the statistics of survival, for, occasionally, these patients do better than the average patient could be expected to do.

If specific questions are asked, it is not unusual to discover a history of previous coronary thrombosis. A number of five- to seven-year survivals have been reported. In a follow-up study of a large group of patients who had had coronary thrombosis, Conner and Holt[2] recorded the survival of one person for eighteen years after what, according to the history, appeared to have been coronary thrombosis. White,[3] in 1933, reported finding, at autopsy, a single scar in the heart of a man of 80 whose history suggested that he had had coronary thrombosis at the age of 63. This man had lived a vigorous life after his coronary occlusion and had been free from heart symptoms until he developed angina pectoris eleven years after the occlusion. The same author,[4] in 1937, reported the survival of a patient for more than twenty-four years after the first coronary thrombosis. There had been an interval of fifteen years' freedom from symptoms between the initial coronary thrombosis and a subsequent series of cardiac infarctions. In the case here reported, the patient enjoyed an even longer interval of freedom from symptoms and duration of life after coronary thrombosis.

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*The average duration of life in 101 cases of coronary thrombosis recently reported by Dr. Francis F. Rosenbaum, Peter Bent Brigham Hospital, Boston, was 41.1 months.

REPORT OF CASE

A telegrapher, whose age was 72 when he was first seen, March 29, 1933, had suffered from angina of effort for five years. He stated that he had experienced the same pain at the age of 40 years, except that at the earlier date the pain had been more severe, and that, over a period of a few weeks, it had gradually increased in intensity, had come at more frequent intervals, and had been more easily precipitated. Finally, an attack of pain did not subside within the usual time, and the administration of an opiate was twice required. He was confined to his bed for two weeks, and said that for another two weeks he felt weak and was unable to work. There was, however, no return of the pain during the next twenty-seven years, or until he had reached the age of 67. At the time of examination he had hypertension and cardiac enlargement. Jan. 15, 1935, he suffered a coronary thrombosis from which recovery was uneventful except for a complicating attack of arthritis. Following this attack the electrocardiogram showed left bundle branch block. He continued to have mild angina pectoris on rare occasions, and obtained easy relief from nitroglycerin. At the age of 77 he retired from his position. April 28, 1938, another coronary thrombosis occurred. This attack was severe, was accompanied by marked pulmonary edema, and was followed by frequent, severe recurrences of pain, and then by cerebral embolism and left-sided hemiplegia. He was confined to bed for four

Fig. 1.—Roentgenogram of heart opened by the Schlesinger method. Right auricle and ventricle situated on the side of the film on which marker is placed. The interventricular septum has been removed and is placed below the heart. The film has not been retouched.

months. Attacks of angina pectoris continued but were infrequent. He had developed prostatic hypertrophy, which caused nocturia, and, unless he was able to void promptly when he awakened in the night, an attack of angina pectoris would result. Because he feared the cardiac pain, he occasionally took nitroglycerin at these times to forestall an anginal attack. He was awakened at 3 o'clock in the

morning of Oct. 2, 1939, with a desire to void, and experienced an attack of angina pectoris which was not relieved by nitroglycerin. A hypodermic injection of morphine was ordered by telephone; a half-hour later he was unconscious, and died within a few minutes.

Before permission for autopsy could be obtained the body had been embalmed; for this reason the heart was considered unsuitable for injection studies. The heart weighed only 360 Gm. The organ was divided by the method of Schlesinger,[5] and a roentgenogram was made. The course of the main branches of the coronary arteries can be quite clearly followed in the roentgenogram, for they are outlined by patches of calcification. Old obstructions, with calcification, were found in the left anterior descending branch, a large branch of the left circumflex, and the right circumflex artery. There were three fair-sized areas of fibrosis in the ventricular walls; the most recent was in the posterior basal portion of the left ventricle. There was no fresh coronary thrombosis to explain the fatal attack.

It seems certain that one of the three scars had resulted from the myocardial infarction which this man had suffered at the age of 40. Following this illness he returned to his usual occupation, and continued to work for thirty-seven years, until he reached the age of 77. For twenty-seven years after his recovery he had no cardiac symptoms. At the age of 67 years he developed angina pectoris, as any man of this age might. When he was 75, another coronary thrombosis, producing bundle branch block, occurred. This illness did not seem to change his physical condition materially after the period of healing had taken place. Three years later he suffered a third coronary thrombosis and was desperately ill for many weeks, but finally recovered. He died rather suddenly from a nocturnal attack of angina pectoris in his eightieth year, nearly forty years after the initial infarction of the heart.

Since we have understood coronary thrombosis for so short a time, cases of long survival could not fall within the personal knowledge of any one physician. It would be necessary to depend upon the patient's history, and to have autopsy corroboration. Coronary thrombosis was formerly wont to masquerade as "acute indigestion," and its true nature was unknown to physician and patient alike. Therefore, a history such as this patient gave would be, of necessity, uncommon. It is suspected that certain middle-aged patients may recover completely from coronary thrombosis and live out their span of life, in spite of the present belief that life is of short duration after cardiac infarction.

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TERMINAL CARDIAC MECHANISM IN CORONARY ARTERY DISEASE*

Report of Two Cases

Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla.

IN NOVEMBER, 1938, Grieco and Schwartz[1] demonstrated that ventricular standstill may be the cause of death after acute coronary artery thrombosis. They did not observe ventricular fibrillation following the ventricular tachycardia which preceded cardiac death. In June, 1939, F. Janney Smith[2] reported, from this clinic, a case in which ventricular fibrillation occurred after acute coronary artery thrombosis. It has been our singular experience to observe electrocardiographically, during one afternoon, the terminal cardiac mechanism in two instances of sudden death from coronary artery disease. One of these deaths was shown, at autopsy, to have been caused by marked coronary artery sclerosis (the patient had had angina pectoris). The other was undoubtedly the result of infarction of the anterior wall of the heart; it occurred on the tenth day following the coronary occlusion.

CASE REPORTS

Case 1.—A. J. A. (No. 79986), a white man, 46 years old, was first seen in June, 1926. On subsequent occasions, in the hospital and outpatient department, he had been treated for a number of minor complaints. No serious illness was noted until Aug. 2, 1939, when he stated that for several weeks he had had severe, aching pain in both shoulders and down both arms. The distress was periodic and would last only a few minutes. It was present only during exertion, and was relieved promptly by rest. It was most likely to occur after meals. There had been no substernal or precordial distress.

On Aug. 11, 1939, abut 3:00 P.M., the patient made one of his regularly scheduled visits to the outpatient department. He had been feeling well and had noted no distress or discomfort that day. In the lobby of the hospital he collapsed, became unconscious and cyanotic, and shortly vomited. He was brought to the cardiac clinic, where he recovered for a few moments and indicated that he was having crushing substernal pain. Concentrated glucose solution (100 c.c. of 20 per cent), with 3.5 grains (0.25 gram) of aminophyllin, was administered intravenously. He soon lapsed into complete coma. The ashen cyanosis increased. The cardiac rate was 54, and the beating was regular. The blood pressure could not be obtained, and the peripheral pulse was imperceptible. He was sweating profusely. An electrocardiogram was obtained. He was given 0.5 c.c. of adrenalin subcutaneously, and heat was applied externally. A pronounced protodiastolic gallop rhythm was present, together with irregularly occurring extrasystoles. The electrocardiograph was again connected. At about 3:15 P.M. a severe clonic convulsion occurred, and respirations ceased. The heart sounds could not be heard, and it was felt that the patient was dead. Artificial respiration was applied, and 1 c.c. of adrenalin was injected into the heart. No further evidence of life appeared except in the electrocardiogram (Fig. 1).

*From the Department of Medicine, Henry Ford Hospital.

Received for publication Nov. 27, 1939.

After 3:15 P.M., when, from the clinical standpoint, the patient was dead, the record first showed an almost regular heartbeat, at a rate of approximately 150, and complexes which varied slightly in contour. Three minutes later the complexes were smaller and varied more. At 3:20 and 3:21 there were prominent, rounded waves which occurred at a rate of 72; they were preceded and followed by very small deflections. At 3:22, there was, for a time, no evidence of ventricular activity, for

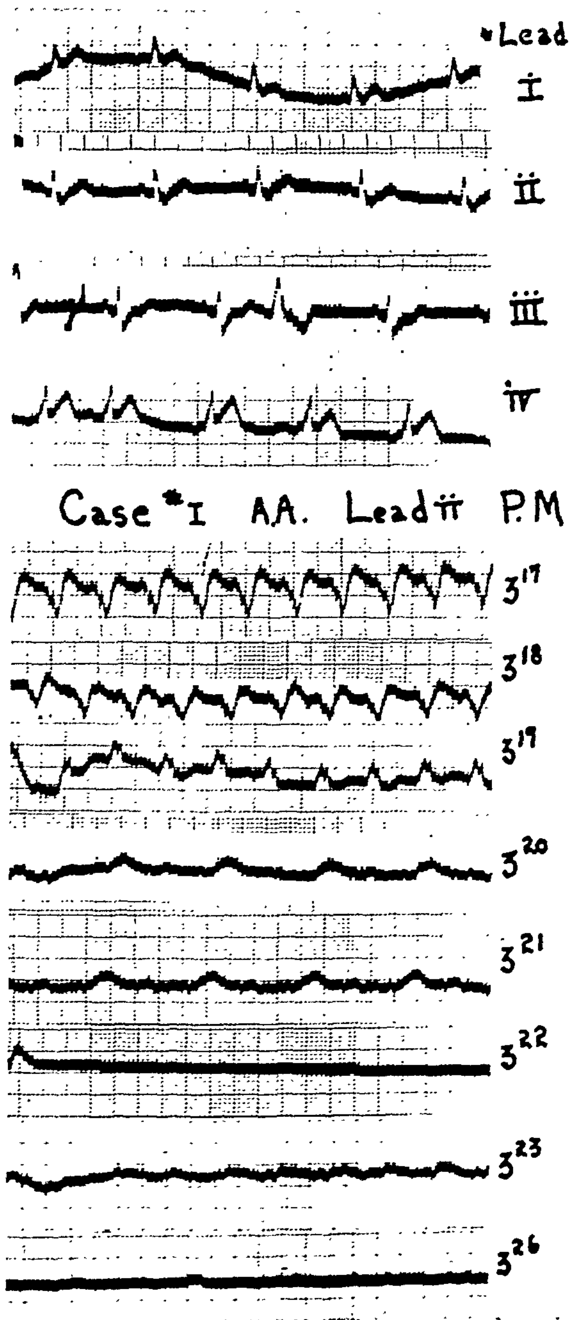

Fig. 1.

the small deflections which occurred at a rate of less than sixty a minute may have been entirely of auricular origin. With the resumption of ventricular activity, at 3:23, although the voltage was small, there continued to be a recurring similarity in the form of the complexes. The last portion of the record showed a further decrease in the amplitude of the deflections.

The autopsy was performed by Dr. G. B. Kerr. The left anterior coronary artery was tortuous and thickened, and the lumen was almost obliterated in several

places by confluent atherosclerotic plaques. No fresh thrombus could be seen. The right coronary artery showed only an occasional patch of atherosclerosis. No area of myocardial infarction could be demonstrated, either grossly or by histologic section.

This was an example, therefore, of sudden death from acute coronary insufficiency, in a case of advanced coronary artery disease. Death occurred within one-half hour after the onset of severe, prostrating pain. Ventricular fibrillation did not occur.

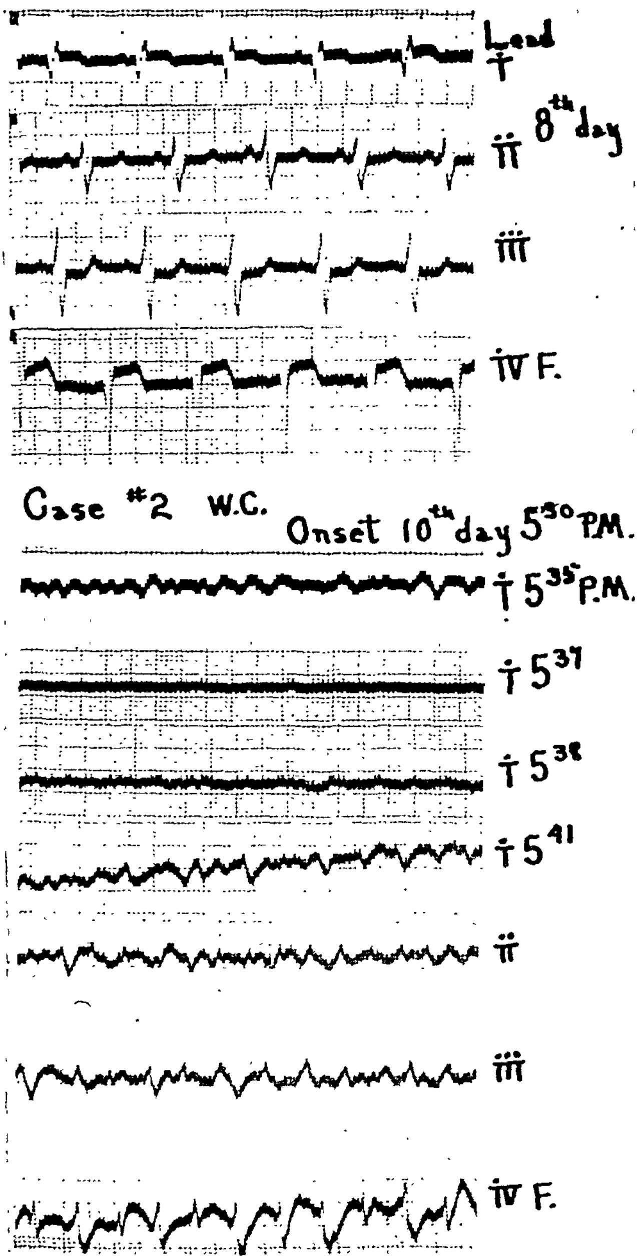

Fig. 2.

Case 2.—Wm. C. (No. 7209), a 60-year-old man, was first seen in August, 1920. Gastrointestinal dysfunction, prostatic enlargement, and fatigability required treatment occasionally thereafter. In 1937, weakness and faintness occurred in brief attacks, and similar sensations were produced by stimulation of the carotid sinus. The electrocardiogram was normal except for slight left ventricular preponderance.

On July 31, 1939, the patient reported that the previous evening, when he was attempting to go to sleep, he noted a sensation of epigastric pressure, and substernal pain which radiated to the jaw. The sensation was transient, and was relieved by sitting up. After four or five attempts, the patient was able to recline comfortably, and slept well. It appeared probable that coronary thrombosis was impending, and the patient was admitted to the hospital, where he spent a comfortable night. No fever, tachycardia, or leucocytosis was present. The following day (Aug. 1, 1939), at 10:30 P.M., the patient suffered severe, continuous, precordial pain, for which he was given morphine, oxygen, and aminophyllin intravenously. The pain persisted, in lessening degree, for twelve hours. The following day the temperature reached 102.8° F. Gallop rhythm, a fall in blood pressure, electrocardiographic changes, and leucocytosis developed. Attacks of nocturnal pulmonary edema occurred despite the fact that the oxygen tent was employed continuously. The electrocardiogram which was made Aug. 9 is reproduced in Fig. 2.

On Aug. 11, at 5:30 P.M., the patient awakened from a restful sleep and suddenly became anxious, restless, and very dyspneic. Within a few seconds the pulse became imperceptible and the cyanosis extreme. The pulse promptly reappeared, and was very rapid; the heartbeat was thought to be regular, and the rate was in excess of 180 per minute. Within less than an additional minute the pulse again faded away, the heart sounds disappeared, cyanosis deepened, and a few gasping respiratory attempts were made. The patient appeared to be dead. An intracardiac injection of adrenalin and massage of the epigastrium had no effect.

The electrocardiograph was connected approximately five minutes after the onset. Sample sections from the continuous record were chosen for reproduction; the time intervals are approximate. The complexes were wide and diphasic, and occurred rapidly and irregularly (ventricular fibrillation).

A post-mortem examination was not permitted.

SUMMARY

A case is reported in which ventricular tachycardia was followed by cardiac standstill; the cause of death was coronary artery disease. This is in support of the contention of Grieco and Schwartz that cardiac standstill should occur as frequently as ventricular fibrillation, and that, if more records could be obtained, additional instances of cardiac standstill would probably be discovered.

A second case, in which ventricular fibrillation occurred during the period of terminal cardiac activity, is added to the five such cases which have been previously reported by others.

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Corrigendum

Attention is called to the republication of the article by Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla., "Terminal Cardiac Mechanism in Coronary Artery Disease" (20: 498, 1940), because of the omission of the last part of the article in the October issue, page 500. The complete article appears in this issue.

Department of Reviews and Abstracts

Selected Abstracts

Scupham, George W., DeTakats, Geza, Van Dellen, Theodore R., and Beck, William C.: Vascular Diseases. A Review of Some of the Recent Literature, With a Critical Review of the Surgical Treatment. Arch. Int. Med. 66: 707, 1940.

In these important annual reviews the authors do not attempt to include all of the available literature on vascular diseases. Many deserving articles have undoubtedly been missed, and consequently the reviews must not be considered complete. Preference was usually given to articles containing original ideas, as well as to those confirming or disproving existing beliefs. Many articles were included on merit alone, or their contents were thought worthy of repetition. The study of vascular diseases is not without its difficulties and is open to criticism. The vast amount of instrumentation is certainly unnecessary for diagnosis; in the majority of cases the history and findings alone are sufficient. Arteriosclerosis, the most prevalent vascular disease, has received too little attention.

This review is always "must" reading.

AUTHORS.

Collins, Dean A., and Hamilton, Angie S.: Pressor Responses Following Short, Complete Renal Ischemia: Characteristics, Mechanism, Specificity for Kidney. Am. J. Physiol. 130: 784, 1940.

Taquini's findings are confirmed; intervals of complete, bilateral renal ischemia of six to seven hours' duration invariably result in elevations of blood pressure when circulation is restored.

Briefer intervals of complete renal ischemia, even those as short as one-half hour, consistently give pressor effects. The magnitude of the responses is only slightly less than that from longer periods.

The characteristics of the response are as follows: The blood pressure rises gradually, reaching a maximum two to nine minutes after the release of the occluding clamps; the elevation is prolonged; in some cases the gradual rise is preceded by preliminary changes, consisting usually of a relatively rapid rise followed by a fall; these preliminary variations are not due to stimulation incident to opening the clamps; the gradual prolonged response is independent of the height of the initial blood pressure.

Occlusion and subsequent restoration of the blood supply of one kidney, either with the other intact or clamped, is followed by a prolonged elevation of blood pressure.

A nervous mechanism is not involved in these responses. This conclusion is based on four groups of experiments: (1) manipulation of the clamps; (2) opening of the clamps with the vessels of the kidney ligated and the accompanying nerve plexuses intact; (3) complete ischemia, with the kidneys and their vessels denervated; (4) complete ischemia, with the thoracolumbar cord destroyed and the vagi cut. The responses must, therefore, be due to pressor material from the ischemic kidney. This material does not exert its pressor action solely, if at all, through the central nervous system.

If the circulation to the leg or to a portion of the liver is arrested for about two hours, no elevation of blood pressure occurs when the circulation is restored.

Neither recent adrenalectomy nor recent splenectomy prevents an elevation of blood pressure following restoration of renal circulation after complete bilateral ischemia.

AUTHORS.

Weeks, David M., Steiner, Alfred, Mansfield, James S., and Victor, Joseph: The Depressor Effect of Spleno-Reno-Pexy on Hypertension Due to Renal Ischemia. J. Exper. Med. **72:** 345, 1940.

In hypertensive dogs with bilateral renal ischemia, unilateral splenorenopexy lowers the systolic blood pressure for as long as nine and one-half months.

Following removal of the fused spleen and kidney, the decreased blood pressure of the dogs with renal ischemia returns to the hypertensive level.

The splenorenopexy produces a collateral circulation between the splenic sinusoids and the capillaries about the renal tubules. The glomeruli are not usually involved in this collateral circulation.

AUTHORS.

Ornstein, George G., and Epstein, Israel G.: Spirometry as a Procedure of Determining Pulmonary Efficiency in Pulmonary and Heart Disease. The Failure of X-rays of the Chest in Estimating Pulmonary Reserve. J. M. Soc. New Jersey 37: 401, 1940.

The use of spirometry is advocated as a simple method of estimating pulmonary reserve and efficiency in cardiac and pulmonary diseases.

By means of spirometry the predicted maximum minute ventilation may be calculated from the actual vital capacity. A formula has been developed to calculate the pulmonary reserve compared to the resting minute ventilation. The normal is a reserve that is ten times greater than the resting minute ventilation.

When the pulmonary reserve is less than six times the resting minute ventilation, symptoms of anoxemia occur. Dyspnea is the chief symptom, and it increases in intensity as the pulmonary reserve falls.

When the maximum minute ventilation (pulmonary reserve) becomes less than four times the resting minute ventilation, the prognosis as to life is bad.

The measured minute ventilation is higher than the calculated normal when the maximum ventilation is reduced in volume.

The roentgenogram of the lungs cannot be used in estimating pulmonary reserve.

AUTHORS.

Holt, J. P.: The Measurement of Venous Pressure in Man, Eliminating the Hydrostatic Factor. Am. J. Physiol. **130:** 635, 1940.

Venous pressure was determined in the supine and prone positions in ten normal subjects, using a modification of the direct method of Moritz and Tabora. Venous pressure values obtained using the reference point of Moritz and Tabora and that of Eyster were markedly different from the values obtained using the reference points of von Recklinghausen, Lyons et al., and the method described here. The reference point of Moritz and Tabora and that of Eyster appear to be placed too far ventrally.

It is suggested that venous pressure be determined in the following manner in order to eliminate the hydrostatic factor. The pressure in the antecubital vein

is measured by the direct method, with the subject in the supine position, the arm lying well below the center of the body and abducted to approximately 45°. The subject is turned over into the prone position and the pressure is measured again, with the arm well below the center of the body and abducted to about 45°. All pressures are referred to the level of the spine as zero. The sum of the two pressures divided by two equals the venous pressure, and the reference point is located at the point in the chest midway between the tops of the two columns of saline in the two pressure measurements.

Venous pressure determined in this manner varied between 7.8 and 14.1 cm. of saline, with results in 80 per cent of the cases varying between 7.8 and 12.1 cm. of saline.

AUTHOR.

Altschule, Mark D., Volk, Marie C., and Henstell, H.: Cardiac and Respiratory Function at Rest in Patients With Uncomplicated Polycythemia Vera. Am. J. M. Sc. 200: 478, 1940.

Measurements of cardiac and respiratory function in patients with polycythemia vera at rest are normal.

The slowing of blood flow, and the symptoms associated with it, are not due to impaired cardiac function but rather to increased resistance to the flow of blood through the small capillaries. This is largely due to increased viscosity of the blood.

AUTHORS.

Arrighi, Federico P.: A New Type of Membrane for Direct Phonocardiography. Rev. argent. de cardiol. 7: 82, 1940.

A new type of membrane for direct phonocardiography is described. It is made of elastic collodion (solution of pyroxilin in alcohol and ether). Once applied on the segmented capsule, it is wrinkled to make it more sensitive and aperiodic.

The membrane thus prepared has good sensitivity, is well dampened, gives good tracings with scarcely any distortion, and may last for years.

AUTHOR.

Buchbinder, W. C., and Sugarman, H.: Arterial Blood Pressure in Cases of Auricular Fibrillation, Measured Directly. Arch. Int. Med. 66: 625, 1940.

The blood pressure has been recorded in cases of auricular fibrillation in man by a direct method.

Fluctuations of blood pressure occur from beat to beat in cases of auricular fibrillation and other irregularities of the heart. The systolic and pulse pressure show a direct relation and the diastolic pressure an inverse relation to the preceding cycle length.

The QE interval was measured and found to shorten with the longer cycle lengths.

The duration of ejection fits the formula $S = K \sqrt{C}$, and in four of our cases in which a curve of means could be drawn, K equaled 0.26, 0.26, 0.26, and 0.23.

In cases of auricular fibrillation and flutter with regular rhythm, the values for blood pressure are nearly constant.

Extrasystoles are found to obey the same relation to the preceding cycle length as that found with auricular fibrillation and flutter, but in their presence additional factors play some role.

These results confirm and extend results obtained with the experimental animal and those in man based on accurate recording of the pulse. They indicate the pulse pressure determines pulse amplitude and that pulse contour is a mirror of the variations in internal pressure during the cardiac cycle at the site where the pulse is recorded.

The results definitely show that it is impossible to obtain accurate determinations of blood pressure by any of the indirect methods when the pulse is grossly irregular.

AUTHORS.

Tinney, W. S., Jr.: Interauricular Septal Defect. Arch. Int. Med. 66: 807, 1940.

Two cases of uncomplicated interatrial septal defect are presented. The respective ages of the patients were 76 and 47.

A review of the literature since 1934 has revealed 22 cases of interatrial septal defect. Roesler's review in 1934 included 62 cases. This brings the total number of cases reported to 86, including the 2 reported here.

The characteristic pathologic features in addition to the septal defect are marked hypertrophy and dilatation of the right auricle, the right ventricle and the pulmonary artery. The left auricle, the left ventricle and the aorta are all relatively small.

The only way to be sure of a correct diagnosis is by roentgen or fluoroscopic examination. There are four characteristic features: increased hilar shadows, great enlargement of the right side of the heart, a small aortic knob and a very large pulmonary conus.

AUTHOR.

Myers, Victor, and Mangun, George H.: Some Chemical Observations on the Human Heart in Health and Disease. J. Lab. & Clin. Med. 26: 199, 1940.

This report deals largely with a discussion of the chemical composition of the heart muscle itself and some of the factors that had been found to influence it. The chemical deficiencies of the myocardium associated with, or resulting from, myocardial insufficiency must constitute limiting factors in the process of recovery. A decompensated heart, although it may be capable of performing a limited amount of work sufficient to maintain the patient in a state of rest, cannot be considered to have recovered, from a chemical point of view, until a complete restitution of the chemical mechanism has been effected.

The chemical substances discussed in this paper by no means encompass the whole realm of possibilities. The number and variety of compounds concerned with the metabolism of the heart are expanding constantly, and new facts are being uncovered which throw light upon the question of how carbohydrates, fats, and proteins, their intermediate products, both in aerobic and anaerobic conditions, supply the energy of contraction. It is indeed possible that somewhere along the way we shall uncover information leading to a direct attack upon the complex problem of myocardial failure.

AUTHORS.

Ernstene, A. Carlton, and Kinell, Jack: Pain in the Shoulder as a Sequel to Myocardial Infarction. Arch. Int. Med. 66: 800, 1940.

The development of persistent pain in one or both shoulders is a relatively common sequel to myocardial infarction. The severity of the condition ranges from the clinical picture of typical periarthritis with intense pain and great limitation of motion to one of mild aching pain with a sensation of weakness but without loss of function. The left shoulder is affected more commonly than the

right, and the symptoms persist for several weeks or months. In a few patients, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with, or subsequent to, the appearance of the symptoms in the shoulder.

The present report is based on seventeen cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarction. In fifteen of these the pain dated from the attack of coronary occlusion or developed subsequent to the attack. In the other two, the patients had suffered from angina pectoris and practically constant pain in both shoulders for a long time before the acute coronary attack. In both of them the pain in the shoulder increased in severity after the occurrence of myocardial infarction. In six of the seventeen cases symptoms of rheumatoid arthritis involving other joints developed either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

After the severe pain of coronary occlusion, certain patients for a long time may unconsciously keep the muscles of the shoulder girdle on one or both sides in a state of abnormal tension as a protecting mechanism against the possible recurrence of pain. Tension of this kind might be expected to be greater on the side to which the pain of the coronary seizures radiated, and this theory would help to explain the relation between the direction of radiation of the cardiac pain and the site of the subsequent persistent symptoms in the shoulder. Once the pain has appeared in the shoulder, continued tensing of the muscles would be natural, and this tension in turn would explain the prolonged duration of the symptoms in so many patients. As matters stand at present, however, there is not sufficient evidence to enable one to state which of the above mechanisms is actually responsible for the development of the persistent pain.

The practical significance of this sequel to myocardial infarction is pointed out.

AUTHORS.

Bourne, Geoffrey: Spontaneous Pneumothorax Simulating Coronary Disease. Brit. M. J., p. 313, Sept., 1940.

Artificial pneumothorax is one of the conditions which clinically may simulate coronary disease. The two cases of spontaneous pneumothorax here described were regarded as being cardiac when first seen. One gave a clinical picture practically indistinguishable from that of coronary infarction, and the other, a picture very much like that of angina of effort.

In the absence of electrocardiographic and radiographic assistance, the diagnosis in such cases may be extremely difficult, for a small partial pneumothorax often gives rise to very slight signs, or to none at all. If the electrocardiograph is the only special means of investigation available, certain other facts tend to complicate the problem; for some cases of coronary disease show no abnormality in Leads I, II, and III, and this is revealed only if a tracing of Lead IV is taken. Again, it is possible for slight coronary infarction to occur even with a normal tracing of Lead IV, either because the lesion is in a ''silent'' area or because it is of small size. Moreover, in some patients with angina of effort the tracing in all leads is normal at first, although later changes may appear. An additional difficulty is the fact that pneumothorax, probably by rotating the cardiac axis, may produce electrocardiographic abnormalities suggesting coronary disease. These are most commonly T-wave abnormalities, S-T deviation from the isoelectric level, and absent or greatly reduced positive initial deflection in the standard Lead IV electrocardiogram.

AUTHOR.

Strauss, Sidney: Delayed Electrocardiographic Changes in Coronary Occlusion. Am. J. M. Sc. 200: 474, 1940.

Five cases are reported in which the diagnosis of coronary occlusion was clear clinically from the start, the electrocardiograms showing changes only after a lag of several days. In one instance the changes were minimal and not definitely *diagnostic without the patient's history.*

An adequate history is all-important in the diagnosis of coronary occlusion, as in all diseases. The diagnosis cannot be left to the cardiographic laboratory alone, *but must be made by the clinician on the basis of all the available data.* Negative or inconclusive electrocardiographic findings do not exclude the presence of a coronary occlusion.

AUTHOR.

Crimm, Paul D., McDonald, J. D., and Cookson, Howard N.: Calcification of Pericardium. J. Indiana M. A. 33: 415, 1940.

A case is presented of a boy, aged 12 years, who had an adhesive pericardium, with marked calcium deposition. The etiological infection was probably pneumococcic. An atypical Pick's syndrome was observed; cirrhosis of the liver was present, with ascites of the abdomen and scrotum, but no edema of extremities. Operative relief was demonstrated to be impossible because of the extensive shell of calcium enveloping the heart.

AUTHORS.

Drummond, C. I.: Calcification of Pericardium. Northwest Med. 39: 217, 1940.

Chronic constrictive pericarditis is not an extremely rare disease, but it is one of the most difficult cardiac conditions to diagnose, due to the lack of uniformity of signs and symptoms. There are certain clues that will lead us to a correct diagnosis.

One case of chronic constrictive pericarditis with calcification is reported, in which diagnosis was made before death. One of the unusual symptoms in this case was edema of the head and neck present in the morning, which subsided after the patient had been sitting up for a few hours.

AUTHOR.

Levitt, Abel, and Jaskiewicz, Stanley J.: Rheumatic Heart Disease. Am. J. Clin. Path. 10: 467, 1940.

The authors have reviewed 110 cases of patients with rheumatic heart disease who have come to autopsy, 58 per cent of whom gave no history of having had rheumatic or antecedent upper respiratory tract infections. A similar percentage died under the age of 50 years. Subacute bacterial endocarditis was observed in 17 per cent of the cases, while syphilitic mesoaortitis complicated the endocarditis in 8 per cent of the cases. In two cases the three types of heart disease—*chronic* endocarditis, syphilitic mesoaortitis, and subacute bacterial endocarditis—were present.

AUTHORS.

Symonds, C. P.: Cerebral Thrombophlebitis. Brit. M. J. p. 348, Sept., 1940.

Mitral stenosis can be diagnosed in a high percentage of cases by careful roentgenologic examination, including fluoroscopy.

The demonstration of a calcified mitral valve is unequivocal evidence of mitral stenosis and also indicates its rheumatic etiology.

Dilatation of the left auricle without general cardiac enlargement is highly presumptive evidence of mitral stenosis.

The diagnosis of mitral stenosis can be made at times by roentgenologic examination, even in the absence of characteristic physical signs herein called "subclinical mitral disease."

AUTHOR.

Altschule, Mark D., and Budnitz, Edward: Rheumatic Disease of the Tricuspid Valve. Arch. Path. 30: 7, 1940.

The clinical syndrome of rheumatic disease of the tricuspid valve is characterized by distention and increase in diameter of all visible veins, hepatomegaly, systolic (and in the absence of auricular fibrillation, presystolic), venous and hepatic pulsations, cyanosis, jaundice, enlargement of the heart to the right, and murmurs over the area of the tricuspid valve. The clinical evidence of cirrhosis of the liver or of congestive heart failure may complicate the picture. The special pathologic condition causing this syndrome consists in insufficiency and variable degrees of stenosis of the tricuspid valve, dilatation of the right auricle and of the veins, and cirrhosis of the liver. The cardiac output is normal when congestive failure is not present. Nevertheless, the venous pressure is elevated, proving that the rise in pressure is due to mechanical obstruction to the heart's inflow of blood. When cardiac decompensation occurs, the output of the heart diminishes and the venous pressure rises above its former high level. The relation of the pathologic and physiologic features of the syndrome to its clinical manifestations is discussed in detail.

AUTHORS.

Stickney, J. Minott, and Keith, Norman M.: Renal Involvement in Disseminated Lupus Erythematosus. Arch. Int. Med. 66: 643, 1940.

The visceral involvement in disseminated lupus erythematosus has been reviewed clinically. The pathologic changes in the kidneys in fifteen fatal cases have been studied. In eight of the fifteen cases there was no definite renal change except that seen terminally in debilitating disease. Without exception, the weight of the kidneys was normal or greater than normal. No contracted kidneys were found.

The most definite lesion was a proliferation of the endothelial cells of the glomerular capillaries. Hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane were also frequently present. These changes are somewhat similar to those which have been described in acute glomerulonephritis and the toxemias of pregnancy. In one case in this series (Case 15) there were pathologic changes characteristic of glomerulonephritis. The relationship of the changes noted to the lupus erythematosus is uncertain, since the renal disease preceded the cutaneous and the cutaneous lesions were inactive during the final illness. In one other instance (Case 4) there was some evidence of a subacute or early chronic glomerulonephritis. In this patient, too, the evidence of renal damage was known to have antedated the onset of the cutaneous lesions. The arteries and arterioles were normal in most of the cases. In several there was slight thickening of the intima, but no thromboses were seen. The changes in the tubules were of a minor nature.

AUTHORS.

Weatherby, Lt. Colonel F. E., and Wiley, Capt. N. H.: Left-Sided Weakness, Blood Pressure Difference Between the Two Arms and Left Optic Atrophy: A New Clinical Syndrome. J. Nerv. & Ment. Dis. 92: 151, 1940.

An unusual syndrome, consisting of left optic atrophy, blood pressure difference between the two arms, and marked weakness of the left arm and left leg, together with slight weakness of the muscles of the right side of the face and the left side of the tongue, is described.

There was no record or history of syphilis, and both blood and spinal fluid were repeatedly negative.

General arteriosclerosis and renal failure to concentrate were present.

There was no clinical or roentgenologic evidence of intrathoracic tumors, aneurysm, or coarctation of the aorta.

Left-sided weakness was greatly ameliorated by the use of a glass suction boot.

Possibilities of an unusual distribution of arteriosclerosis and of an unknown disease of the brain are suggested.

AUTHORS.

Braun-Menendez, E., Fasciolo, J. C., LeLoir, L. F., and Muñoz, J. M.: The Substance Causing Renal Hypertension. J. Physiol. 98: 283, 1940.

The pressor and vasoconstrictor properties of the venous blood from kidneys in acute ischemia have been studied. Extracts of this blood contain a pressor substance (hypertensin) which is also formed in vitro when blood proteins are incubated with renin.

Some chemical and pharmacologic properties of hypertensin have been studied and found to be different from those of other known substances.

Experiments are reported which indicate that renin is an enzyme, blood pseudoglobulins the substrate, and hypertensin the reaction product. Hypertensin disappears if the reaction is permitted to go too far, and it is also inactivated by other proteolytic enzymes and by blood.

The pressor action of renin appears to be due to the formation of hypertension in blood; and a similar mechanism is suggested for arterial hypertension due to renal ischemia.

AUTHORS.

Crabtree, E. Granville: Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension. J. Urol. 44: 125, 1940.

A high percentage of pregnancy pyelonephritis patients show evidences of renal damage after five to eighteen years. The renal insufficiency had not progressed to the point of elevated nonprotein nitrogen in but one of the cases studied, the case of toxemia and pyelonephritis.

Hypertension was present in eight of seventy-two cases of pyelonephritis and in all of those that were complicated by toxemia. The relation of hypertension to the degree of renal damage was not always constant, but there was a closer relation of hypertension to the cases which showed marked renal insufficiency than to those which showed lesser degrees of damage to the kidneys. Hypertension is not the rule in cases of pyelonephritis pregnancy at from five to eighteen years after the infection.

Many of the patients studied appeared to be in excellent health.

AUTHOR.

Palmer, Robert S., Chute, Richard, Crone, Neil L., and Castleman, Benjamin: The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis, as Revealed by Intravenous Pyelography. New England J. M. 223: 165, 1940.

Forty-seven (22 per cent) of 212 patients with continued arterial hypertension not due to glomerulonephritis showed congenital or acquired deformities of the pelves or ureters by urography.

The deformity in the pyelogram was unilateral in thirty-four (72 per cent) of these forty-seven cases, or 16 per cent of the 212 cases studied.

Such deformities are often incidental, but if significant in the etiology of the hypertension, probably represent a participating or precipitating rather than a major factor.

Surgical removal of the presumably offending organ in nine cases resulted in marked improvement in the blood pressure and the symptoms for one year and ten months in one case, although this patient still remains definitely hypertensive.

In cases of unilateral renal disease associated with persistent hypertension, the decision to remove the affected kidney, with the hope of curing or modifying the course of the hypertension, is based on three assumptions: that the lesion is not incidental; that there is no vascular disease in the remaining kidney; and that one will not be faced with recurrent pyelitis in the remaining kidney.

AUTHORS.

Ochsner, Alton, and DeBakey, Michael: Peripheral Vascular Disease. Surg., Gynec. & Obst. **70**: 1058, 1940.

The bases for rational therapy in peripheral vascular disease are discussed.

Peripheral vascular disease merely signifies a disturbance or actual diminution in the normal amount of circulating blood to a part and is usually the result of a varying diminution in the normal caliber of the peripheral vessels. This decrease in intraluminary volume may be caused by obliterative structural change, by abnormal spasticity, or by both, depending upon the type and stage of the disease.

Effective therapy aims at improvement in circulation or increase in blood supply to the part; this cannot be accomplished by an attack upon vessels that have already undergone structural change. Vasospasm, on the other hand, is a physiologic or functional derangement which can be influenced satisfactorily by appropriate therapy.

Because vasospasm is the one controllable factor, the determination of its presence or absence and its extent are of decisive importance.

Therapeusis in peripheral vascular disease consists of measures aimed to improve the peripheral circulation and may be divided into two large groups: (1) conservative measures; and (2) radical procedures.

Conservative measures are indicated in all cases of peripheral vascular disease except in acute vascular catastrophes and in the rapidly progressive peripheral vascular disturbances. The conservative measures consist largely of two groups: (1) those which are directed toward the elimination of all factors which increase vasospasm; and (2) those factors which produce vasodilatation. Of the former, emotional disturbances, environment, and tobacco are the most important. Of the latter, application of heat and rugs and the performance of vascular exercises are the most significant.

Whereas many of these conservative measures are justified and are usually sufficient to produce complete relief of symptoms, in the rapidly progressive case, and especially in the case associated with a prominent degree of vasospasm, at-

tack upon the sympathetic nervous system is considered desirable. The concept that in these vasospastic states, sufficient vasoconstrictor impulses are transmitted over the sympathetic pathways to cause diminished circulation and that the release of these impulses may be enough to permit the return of circulation to normal forms the rational basis for sympathectomy. Interruption of impulses over sympathetic pathways may be accomplished by chemical block or by resection.

Chemical block of the regional sympathetic ganglia in peripheral vascular disease is considered a conservative procedure because of its efficacy, its simplicity and facility of performance, and its economic advantages.

In the presence of marked vasospasm in patients with impending vascular catastrophes or in those in whom conservative measures fail to relieve the vascular manifestations, radical therapy is justified. Sympathetic denervation of the affected part, however, should be performed only after the demonstration of vasodilatation following the diagnostic test of procaine hydrochloride block.

The factors which have been considered for the comparative failure of cervicothoracic sympathectomy to maintain chronic vasodilatation are reviewed and analyzed critically.

The technical considerations in the performance of cervicodorsal and lumbar sympathectomies for peripheral vascular disease are reviewed historically, described, and illustrated.

AUTHORS.

Symonds, C. P.: Cerebral Thrombophlebitis. Brit. M. J. 2: 348, 1940.

In all except one of the cases related in this paper, visible proof of the diagnosis of thrombophlebitis was lacking. The clinical symptoms, however, exactly resemble those which have been recorded in cases (most of them following lateral sinus thrombosis from otitis media) in which the diagnosis has been proved post mortem. It appears probable that cerebral thrombophlebitis by direct extension from an infective source or occurring as part of a generalized tendency to thrombophlebitis is not very uncommon and frequently runs a benign course. Such cases in the past may have been erroneously attributed to arterial thrombosis or embolism, or to encephalitis. Some, especially those in which the onset accompanied focal epileptic attacks, have doubtless been diagnosed as meningitis or abscess. The latter diagnosis has led occasionally to unnecessary and probably harmful operation. In Case 4 the diagnosis was so much in doubt that it needed an exploratory craniotomy to satisfy physician and surgeon that the patient would make a spontaneous recovery. For these reasons, and in the hope that they may stimulate further inquiry, it has seemed worth while to record these few observations.

AUTHOR.

Steinberg, Israel, Robb, George P., and Roche, Ursula J.: The Differential Diagnosis of Mediastinal Tumor and Aortic Aneurysm. Value of Contrast Cardiovascular Visualization. New York State J. Med. 40: 1168, 1940.

Four cases are described which illustrate the practical value of visualization of the intrathoracic blood vessels in the differential diagnosis of aneurysm and tumor of the mediastinum. A metastatic carcinoma in the right side of the mediastinum and a primary sarcoma in the left side strikingly simulated aneurysm of the ascending and descending portions of the aorta, respectively. Visualization of the great blood vessels, however, revealed or confirmed the presence of aortic aneurysm in the latter cases and excluded intrinsic gross abnormality of the aorta in the other two instances.

AUTHORS.

Bourne, Geoffrey: Examination of the Heart in Recruits. Brit. M. J. 2: 442, 1940.

The routine examination by the medical boards of many healthy young men called up for military service has brought into prominence various physical signs and symptoms referable to the heart. These are often slight, but their presence raises questions as to whether they can be ignored or whether they are important enough to justify the rejection of the man as unfit for service or his relegation to an inferior physical category.

Cases met with can be divided into three groups:

1. The heart is normal in size and shape when examined radiologically; no symptoms are present, but minor variations in the heart sounds cause suspicion of disease.

2. The heart is normal clinically and radiologically, but the history or symptoms suggest present or potential effort syndrome or neurocirculatory asthenia. These men, if passed for full active service, are likely to break down and to become a prolonged and severe charge upon the community and upon themselves. An attempt should be made to pass the slighter cases for clerical or other nonviolent work, or to find them official work similar to that which occupies them in civil life.

3. Exercise tolerance is normal, but physical abnormalities of the heart, either congenital or acquired, are detected. The diagnosis of the more common congenital abnormalities is described and an attempt is made to indicate the manner of dealing with the organic cases.

AUTHOR.

Flaxman, Nathan: Pregnancy and Heart Disease. Am. J. Obst. and Gynec. 39: 814, 1940.

An analysis of the life cardiac histories of forty-nine women with organic heart disease who delivered from one to twenty-two children (average 4.9 pregnancies) as compared with the histories of forty-one nulliparous women with similar cardiac lesions, revealed that there was little or no difference in the known duration of the heart condition, in the ages at the onset of myocardial failure, or in the ages at death.

The heart lesions were recognized earlier in the parous women, mainly because of the pregnancies. In women with compensated rheumatic heart disease, pregnancy may be undertaken without any added risk. However, it is suggested that women with compensated heart disease be advised to marry early and bear children before the age of 25, if they desire a minimum of risk. In this way, also, they can have a longer period in which to rear their children. Women with heart disease die early because of the natural evolution of the cardiac disturbance and not because of the childbearing.

AUTHOR.

Brown, Clark E., and McNamara, Delbert H.: Acute Interstitial Myocarditis Following Administration of Arsphenamines. Arch. Derm. and Syph. 42: 312, 1940.

A case of acute interstitial myocarditis complicating exfoliative dermatitis due to neoarsphenamine is reported. A similar case is reviewed in some detail, bringing the total cases reported to eight.

The probably allergic etiology of the myocarditis is discussed, although the exact nature of the allergen is not apparent.

AUTHORS.

Book Review

ATLAS OF CARDIOROENTGENOLOGY: By Hugo Roesler, M.D., Associate Professor of Roentgenology, Temple University School of Medicine, Philadelphia, 124 pages, 166 figures, Charles C. Thomas, Springfield, Ill., 1940. $8.50.

Superficially, the atlas method of presenting the subject of roentgenologic diagnosis appears to be an ideal one, yet it has not been notably successful in the past. In large part, this is because of the impossibility of illustrating even a small percentage of the innumerable variations in the roentgenographic appearance of the normal and pathologic anatomy of any structure. If one is to understand roentgenology, certain rules must be learned and certain details mastered. The temptation to interpret one roentgenogram in terms of another, seen on a previous occasion, or illustrated in a book, is strong enough; the possession of an atlas may, unfortunately, encourage this type of ''snapshot'' diagnosis.

With respect to diseases of the heart, these strictures are much less applicable, particularly in the case of this atlas. If used properly, that is, as a supplement to the author's text on the roentgenologic diagnosis of cardiac diseases, this volume should prove most valuable. A series of cases is presented, for each of which there are a well-written summary; reproductions of the roentgenograms; in many instances, photographs of the anatomic specimen; and many well-conceived diagrams to illustrate the normal and abnormal heart. Almost all of the various types of cardiac abnormalities are exhibited, and the discussions are sufficiently detailed to bring out the vital points in roentgenologic diagnosis. The author has described, very clearly, the anatomic relationships of the heart, the significance of the various curves and borders which are seen in the roentgenogram, and the effect of the pathologic physiology of cardiac disease upon the roentgenogram. In many respects, the comparison of the roentgenogram with the unique coronal dissections of the heart is the most valuable contribution of the atlas.

The format and printing are unusually fine, but the many expanses of blank white paper give an uncompleted appearance which is disturbing. Considering the size and cost of the atlas, 166 figures seem scarcely adequate. Although certain disease processes are well elaborated, notably the effects of emphysema upon the heart, the number of illustrations for the majority of cardiac lesions is insufficient. The demonstration of a case of ''funnel'' chest, without indication of the characteristic displacement of the heart to the left, is an omission. The textual material itself leaves nothing to criticize. Both the cardiologist and the roentgenologist will benefit greatly from a careful and repeated study of this splendid addition to the library of works on diseases of the heart.

LEO G. RIGLER

Announcement

Beginning January 1, 1941, the yearly subscription price of the AMERICAN HEART JOURNAL (two volumes) will be as follows: United States, its Possessions, and Pan-American Countries, $10.00; Canada, $11.50 (in Canadian currency); and Foreign Countries, $11.00. The price of journal membership in the American Heart Association will be raised from $10.00 to $11.00 per annum. These changes will not affect subscriptions or American Heart Association journal memberships which are already in force, but will apply to all new subscriptions and to renewals.

These increases have been made necessary by rising costs of production, but they will also enable the publisher to increase the size of each issue by sixteen pages, which will add a total of 192 pages to the two annual volumes. It is earnestly hoped that this additional space will make it possible to reduce to six months, or less, the interval between the receipt of manuscripts and their appearance in print.

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THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*

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Original Communications

NOMENCLATURE AND DESCRIPTION OF THE ELECTROCARDIOGRAM

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New York, N. Y.

THERE is at present a regrettable confusion in the application of Einthoven's terminology for the peaks of the electrocardiogram (Hurxthal,[1] Shookhoff and Douglas,[2] Vega and Quero[3]). This is especially true of the QRS group, and, to a lesser extent, of the T wave. It is unfortunate that our terminology should be indefinite, for the method most used for describing and comparing the curves involves measurement of the height of the peaks. It is necessary, therefore, that the peaks be similarly named by all who are studying them; for this reason, I wish to suggest the adoption of certain principles of nomenclature which can be readily applied.

Einthoven at first designated the usual, large, upward deflection of the QRS group as R, and applied the term Q to the downward deflection which often preceded it, and S to the downward deflection which often followed it. When he came to compare records obtained by three leads from the same subject he encountered difficulties in applying this terminology to the peaks which appeared in the different leads. It was apparently his idea at this time that R should be the name of the most prominent peak of each lead, and that the terms Q and S, respectively, should be applied to the portions of the QRS group preceding and following this peak. He referred repeatedly to the most prominent peak in Lead I or Lead III as an R wave, even when this peak was directed downward, and occasionally referred to an upward Q or S wave. In 1908, he[4] published the figure, reproduced here as Fig. 1, which shows an upward Q_3 and a downward R_3. In this same article he suggested that the formula Lead II − Lead I = Lead III might be used for the identification and naming of the corresponding peaks in the different leads. He stated that "although this method might appear simple enough, yet difficulties would arise in applying it, especially because the waves indicated by the same letters often fail to occupy identical phases of the heart cycle."

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Quite evidently he recognized at this time the fallacy of supposing that similarly named peaks in different leads would always arise from the same potential produced by the activity of the muscle. Possibly it was the further development of this thought which led him,[5] in 1916, in referring to Lead III of a record with typical left axis deviation of QRS, such as Fig. 1, to say that "inasmuch as there is no reason to regard this large negative peak (in Lead III) as either R or S, we encounter a real difficulty in searching for the similarly named peak in the other leads. We avoid this difficulty if we consider the QRS group as a whole, and take the highest or lowest point of the group in the three leads as the object of our measurement." The measurement referred to was to be used for determining the electrical axis of the most prominent peak of the QRS group. In his later writings he showed little inclination to name the individual peaks. Among the illustrations of his Harvey Lecture, in 1924, he included a record in which Lead I and Lead III were quite similar to those of Fig. 1, and marked the QRS group of Lead III simply as QRS, in spite of the fact that naming the peaks would not have been difficult in this case if his original procedure of calling the largest deflection R had been followed.

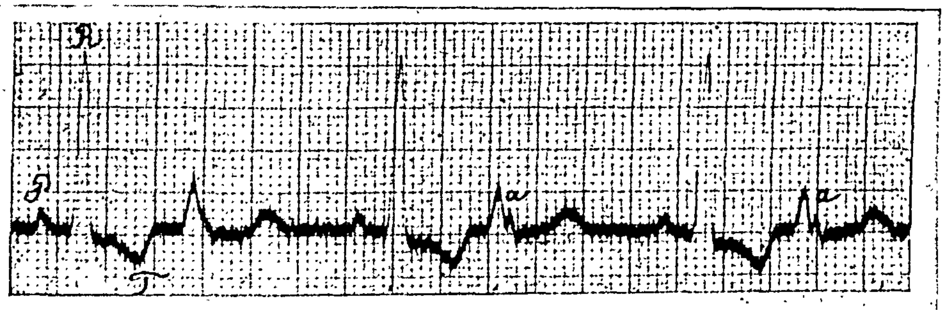

Fig. 40. *S. K.* Atypische Herzkontraktionen. Ableitung I.

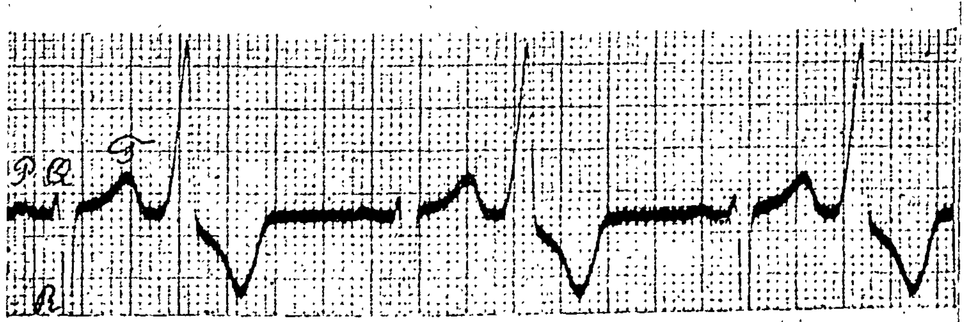

Fig. 41. *S. K.* Atypische Herzkontraktionen. Ableitung III.
Absz. 1 mm = 0,04 Sek. Ordin. 1 mm 2 × 10^{-4} Volt.

Fig. 1.—Showing Einthoven's early use of the nomenclature of the QRS group (from Weiteres über das Elektrokardiogramm, *Arch. f. d. ges Physiol.* 122: 517, 1908). Note particularly the upward Q and downward R in Lead III.

Einthoven's terminology, as he first used it, seemed to imply that peaks of the same name in different leads should represent the same current within the heart. As he himself pointed out, however, this

implication was not justified, for the different peaks of the QRS group in the three leads rarely occur at exactly the same instant during the cardiac contraction, and are sometimes markedly separated in time. The similar name does not indicate the same action current of the heart. This feature may be demonstrated clearly if two or more leads are taken simultaneously. Fig. 2, which is reproduced from Einthoven,[6] affords an excellent example of how peaks named alike by Einthoven's method may fail to represent synchronous portions of the QRS group. The peaks of Q_2 and Q_3 occur during the ascent of R_2, and when R_3 has reached only half of its height. The peak of S_1 occurs when the descent of R_2 is only half completed, and the total duration of S_1 is represented in the descending portion of R_2.

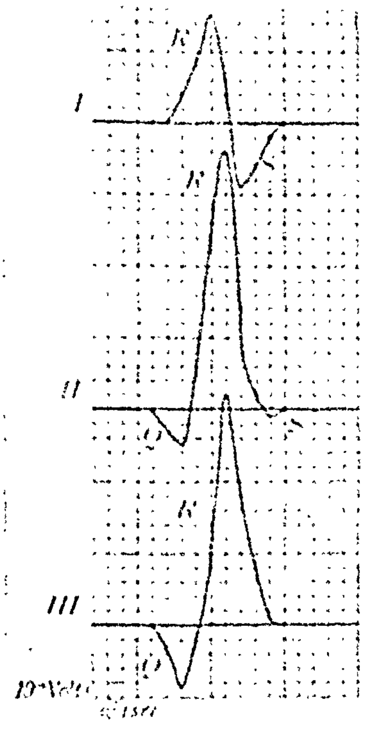

Fig. 16 Konstruktion der *QRS*-Gruppe von Fl. bei den drei Ableitungen. Jede Ordinate entspricht identischen Phasen einer Herzperiode. Abszisse 1 Skalenteil = 0,01 Sek.; Ordinate 1 Skalenteil = 10^{-4} Volt.

Fig. 2.—Construction of the QRS group by the three leads. (From *Arch. f. d. ges. Physiol.* 150: 291, 1913.)

Einthoven's nomenclature, in this record, would apply the name S to a peak in Lead I resulting from potentials which are a part of R in Lead III, and the name Q, in Leads II and III, to peaks resulting from potentials which are a part of R in Lead I. It also fails to indicate, by name, the deflections in Leads II and III caused by the potential which produces S_1, or to indicate in Lead I the potential which produces the deflections Q_2 and Q_3. In each case, the value in question is repre-

sented in the ascending or descending limb of the R wave. It would have been evident that this was the case if Einthoven's formula of lead values had been applied to the standard electrocardiogram of this patient. The negative value of Q_3 must have a corresponding positive value in Lead I of at least the difference between Q_3 and Q_2, and the negative value of S_1 must have a corresponding positive value in Lead III of at least the difference between S_1 and S_2. Thus, the manner of development of the heart's potential can often be roughly ascertained by the application of Einthoven's formula to the peaks of the three leads, and the actual names which he would have applied to the peaks do not give additional help in understanding it. On the contrary, if they be taken too literally, the impression that like names in different leads represent like potentials will actually become misleading. It is possibly for this reason that he came to avoid naming the individual peaks, and to speak of the QRS group as having its "chief deflection" in one or another direction.

Lewis and Gilder,[7] in 1912, published a series of measurements of human electrocardiograms, and, in this report, as well as in his other writings,[8] Lewis deviated somewhat from Einthoven's usage in lettering the peaks of QRS. He indicated only downward peaks by the letters Q and S, and only upward peaks by the letter R. With this method of naming the peaks, the upward deflection of Lead I might be called R, while a corresponding, synchronous, downward deflection in another lead, caused by the same potential, might be called either Q or S, depending upon whether it preceded or followed the upward deflection of that lead, which would be called R. When the upward deflection was notched, or when there were two upward peaks, Lewis simply called the deflection a notched wave.

Lewis' method of lettering the peaks failed, as did Einthoven's, to take into account the potential contributing to the ascending and descending limbs of the deflections. It differed from Einthoven's earlier ideas in that it avoided any suggestion of giving the same name to related potentials in different leads. It was a purely arbitrary terminology which carried only an implication of direction, whether upward or downward, and, in the case of the terms Q and S, of time relative to the upward deflection, which was always called R.

Although Einthoven's method was more widely used at first, the majority seem to have preferred to follow Lewis' frankly arbitrary method of naming the individual peaks, rather than Einthoven's more superficially logical one. Although some have objected that Lewis' method also may interfere with an understanding of the events of the QRS group because the same potential may cause peaks with different names in different leads, no such confusion should arise if the nomenclature is understood to be entirely arbitrary and not to imply any relationship between peaks of the same name. In such an arbitrary system there must not be any implication that similar names have a

similar clinical significance, for then, in occasional cases, when the clinical significance is not the same, we find ourselves in a quite illogical position. Because Einthoven's method, as he first used it, implied that similarly named peaks have a similar origin, and because it can be demonstrated that such peaks in different leads do not usually have a similar origin, it seems best to avoid Einthoven's method of naming these peaks, and follow Lewis' simpler and more arbitrary method of applying Einthoven's letters.

Neither of these authors continued to expand his terminology sufficiently to indicate how it should be applied to certain unusual varieties of QRS which are encountered. It seems necessary that this should be done in order to avoid further confusion; and, therefore, an expansion of Lewis' modification of Einthoven's electrocardiographic terminology is here submitted.

A QRS group with two upward peaks separated by a downward one has commonly been referred to as an M-shaped complex. Likewise, when there are two or more upward peaks and two or more downward ones, the term vibratory QRS group has often been used. These terms are sufficiently descriptive to be easily applied, and may be useful for general purposes, but they make it impossible to refer to the extra peaks specifically, or to measure them. It is therefore suggested that, when more than one upward deflection appears, the first should be called Ra, and the subsequent ones Rb, Rc, etc., as occasion arises. A downward deflection preceding the first R would be referred to as Q, and the first downward deflection following the first upward deflection would be called S if there were only one, and Sa if there were more than one. Subsequent downward peaks would be called Sb, Sc, etc., as in Fig. 3.

In describing precordial leads, the same arbitrary terminology of QRS can be applied with equally satisfactory results if it be clearly understood that here the peaks of the same name are even more dissimilar in origin than in the standard leads. Nor need records from patients with congenital dextrocardia lead to confusion, for Lead I is just as truly a reversal of the ordinary Lead I if we call the first deflection Q and the second R as if we called them inverted R and S waves, respectively. To do the latter is not, in our opinion, good practice, for it implies that the names of the peaks have a definite meaning.

There has not been a proper agreement as to the naming of the waves of a QRS group like those in Fig. 3*C*, which shows, first, a very small upward deflection, i.e., 1 mm., or less, followed by a sizable downward peak and another upward peak. Some would disregard the small, initial, upward peak and call the downward one Q and the second upward one R. There is a very real objection to this procedure, in that it demands a definition as to exactly what size must be reached by the initial deflection before it may be called R. It seems more simple, and, therefore, better, to call any upward deflection R, and to name the other peaks in proper sequence. To call such a QRS an M complex is unsatisfactory, as has been said, because this does not allow of measurements.

Usage is also divergent when the QRS group is entirely below the isoelectric level, with no upward peak which could be called R, as in Fig. 4*D* and *E*. This downward peak has previously been called S[9], because in limb leads such records are most frequent with right or left axis deviation of QRS, and because the downward peak in Lead I with right axis deviation, and, in Lead III, with left axis deviation, is usually an S. This S is often preceded by a small R and as in Fig. 4*C*, such an R may disappear during one phase of respiration, leaving only a downward deflection. It is because of the frequency of such records, and because they are often associated with ventricular hypertrophy caused by valvular disease, that the author has previously advocated the use of the letter S for the peak of a QRS group which has no upward deflection. Such records are obtained almost as commonly from patients with valvular disease as from patients with coronary arteriosclerosis. In a group of seventeen such records, selected from a large clinic series, seven were from patients with disease of the mitral or aortic valve, or both, and the remainder from patients with coronary arteriosclerosis or hypertension. Furthermore, Durant, who called such a QRS group Q, has found that if patients with such records are excluded from a group in which Q_1 is large, more patients with valvular disease will be excluded than will remain.[10]

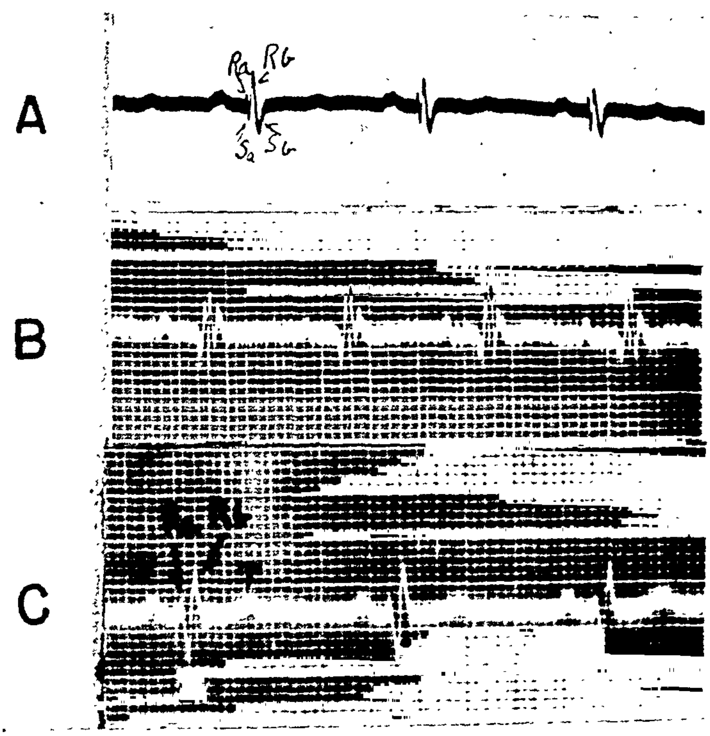

Fig. 3.—Illustrating the nomenclature of M complexes in *C* and of the vibratory QRS group in *A* and *B*.

In spite of the above considerations, many physicians have called such a wave Q, thinking that it warrants this title because it is the first downward deflection of QRS. Neither Einthoven nor Lewis used the letter Q

in this way; both of them designated Q as a downward deflection which preceded R. Also, it has been suggested that these waves should be called Q because they are often found in clinical conditions which are likely to be associated with well-marked Q waves followed by an R. This reason violates the principles of an arbitrary nomenclature. In view of the present divergent usage in naming these downward QRS deflections, it seems very important to reach an agreement. This downward deflection, like any other QRS group, contains the elements of the Q, R, and S which may appear in other leads of the record. It seems

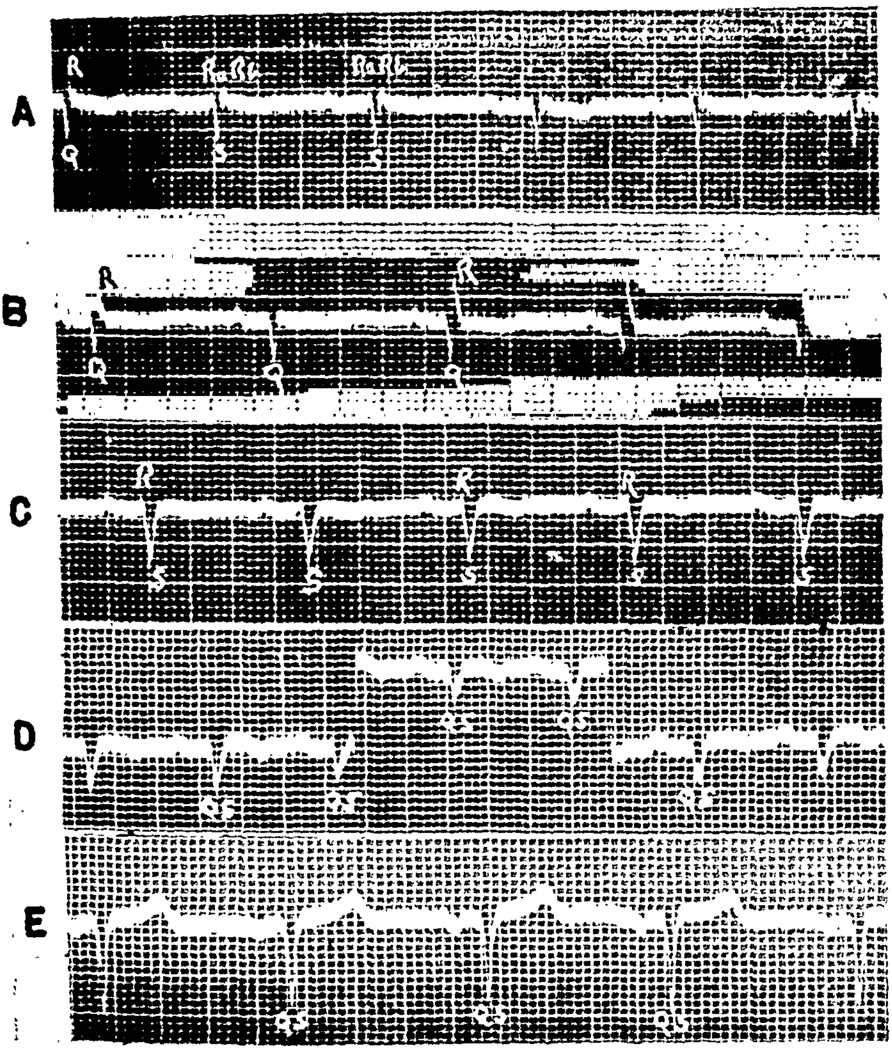

Fig. 4.—The nomenclature of downward deflections. Records *A* and *C* show downward waves which should be called S. Record *B* shows downward waves which should be called Q. Records *D* and *E* show downward waves which should be called QS.

advisable, because of the current lack of agreement concerning the name for such waves, and in order to distinguish them from others whose apices are followed by an R wave, or are preceded by an R wave, to call these deflections QS. This would indicate that they contain the elements of both peaks, and that there is a possibility that in records taken at

another time a small R might appear and indicate definitely which name should have been attached to the wave; moreover, it may be possible, by thus separating these records from those with a definite Q (followed by R) and a definite S (preceded by R), to come to understand more clearly what their clinical significance may be.

If it is to be called QS, there must not be any upward deflection, no matter how small, either preceding or following this downward wave. If such a deflection precedes, as in Fig. 4*C*, the downward peak must be called S. If a small upward deflection follows it, as in the first cycle of Fig. 4*A*, it must then be called Q. In records with a small R which appears and disappears with respiration, the disappearance of R may lead to a change of the name of the downward deflection, as in Fig. 4*A*, *B*, and *C*. In order to avoid this, it is advisable to retain throughout the lead whichever name, Q, S, or QS, would belong to the downward deflection in the majority of the complexes.

The use of the term notching should be restricted to doubled or split waves, the peaks of whose notches do not cross the isoelectric level. Should the isoelectric level be crossed, each of the resulting peaks should take a name of its own, as in Fig. 3*A*. Notching of the QRS group is an important feature and should be described exactly. It should be stated that it occurs at + or – so many millimeters on the descent or ascent of the wave, and the lead should be designated, e.g., at –5 mm. on the descent of S_2. This exact description is needed, for it has been observed that notching of QRS in certain situations in relation to the peaks is commonly associated with myocardial damage.

Lesser grades of disturbance of the course of the ascending or descending limb of a peak are called slurring. With this in mind, the normal form of the peaks or QRS must be especially noted; often the first deflection, as it turns away from the P-R level, does so in a rather gradual slope, and the line at this point is broader, and therefore more slurred, than the subsequent course of the wave, which becomes more abrupt and steeper in its further course toward the peak (R_1, Fig. 1; QS wave, Fig. 4*E*). At the peak of a wave the rate of ascent or descent usually is less abrupt than in the remainder of its course, so that one often sees, just before or after the peak, or perhaps in both places, a thickening of the line to which the term slurring may be applied, as in R_1 of Fig. 1. In other records a deflection of small size will produce what appears as a rather uniformly thickened line, when compared to the thinness of the line producing larger deflections. This may be observed in R_3 (Q_3) of Fig. 1 and in the first downward deflection of Fig. 3*B*. Since this is a uniform thickening of the line, it may not be comparable to those thickenings which occur in only a portion of one side of a wave, but until more definite knowledge on this point is available, it seems best to apply the term slurring to this feature. As QRS comes to an end at the R-T

or S-T transition, the slope is often more gradual and the line more slurred than in other portions of the peak. This is seen in R_1 and S_3 (R_3) of Fig. 1.

It is known that slurring of the peak of a wave or at the beginning or ending of the QRS group may occur normally, so that the location of the slurring must be noted as an aid in deciding whether it has any pathologic significance. It should be described in a manner analogous to that used for notching, namely, that it is found a certain number of millimeters from the zero level and on the ascent or descent of a certain wave. In the present state of our knowledge it is possible to attach *more definite significance to slurring which does not occur at one of the* three normal sites than to that which does. We cannot distinguish the borderline between a normal and an abnormal degree of slurring in these normal locations.

The "duration of the QRS group" has not been subject to misinterpretation, but insufficient attention has been paid to the fact that the duration varies in different leads. Reference to Fig. 2 will show that the duration of QRS is shorter in Lead I of this record than in Leads II and III. Inasmuch as the duration of QRS indicates how much time it takes for the contraction wave to spread over the ventricular muscle, the longest QRS in any given electrocardiogram must be the nearest approach to the actual time of spread. If QRS is shorter in one lead than in another, it must be because a portion of the QRS group is isoelectric in that lead, as in Lead I of the figure. Inasmuch as different records will be found to show the longest QRS in different leads, it is obvious that no one lead can be selected to indicate the duration of the QRS group, and that it should be measured in all leads and the longest measurement used. The duration of the R wave alone, will, of course, have little physiologic significance.

Similar considerations lead to the conclusion that measurements of the duration of any part of the electrocardiogram should be made in all three leads, and that the longest measurement should be taken to indicate the actual duration. This applies to the P wave, the P-R interval, QRS, the Q-T interval, and the T wave. In following this procedure, occasional records will be found in which the P-R interval is prolonged by 0.01 or 0.02 sec. because of the inclusion of an initial isoelectric portion of QRS in this interval. Such is the case in Lead I of Fig. 2. It may be suspected in clinical records when one lead shows a shorter QRS duration and a longer P-R interval than the others.

The QRS group passes over more or less abruptly into the T wave. The portion of T immediately following the R-T or S-T junction has often been referred to as the R-T or S-T interval or segment. For purposes of nomenclature we may speak of this as the S-T junction or segment, irrespective of what name may be applied to the last peak of QRS, just as we speak of the P-R interval, irrespective of the name of the first peak of QRS. The ending of the S-T segment cannot be definitely

indicated, for it passes quite gradually into the peak of T. It is actually the first limb of the T wave. It seems important from the point of view of nomenclature to refer to the whole of the final deflection as the T wave, and to speak of its beginning as the S-T junction.

In most electrocardiograms the S-T junction is effected by a definite change in the inclination of the curve toward the isoelectric level, so that within less than 0.01 sec. the R or S wave may be said to end and the T to begin, forming a more or less sharp angle at this point. Other electrocardiograms may show a gradual change in the inclination of the curve, so that R or S, as in Fig. 1, may curve gently into the beginning of T, sometimes taking 0.04 sec., or more, to complete the transition. These two types of S-T junction are not separate and distinct, but represent the two extremes of the various forms which may be encountered; various degrees of sharpness of the resulting angle at the junction will be observed. One or more leads of the record may show a sharp S-T *transition and the remainder a less sharp transition. If, however*, several cycles are carefully inspected, it is usually possible, as a result of the variations in the complexes which occur with respiration, to discover in even the most gradually curved transition a point which may be called the S-T junction.

This junction should be described as being positive or negative, in relation to zero. Special attention should be given to an observation made by Lewis, in 1912. The deflection of the P-R level is caused by auricular activity which continues, although diminishing, for 0.36 sec., or more, after the beginning of P, so that this in effect establishes a new zero level for the deflections of the QRS group and the S-T junction, from which new level their deflections should be measured. Usually, this deflection is less than 1 mm., but in certain records it may reach a magnitude which makes it important.

Having described the position of the S-T junction in relation to this zero, we must still describe the T wave, i.e., the whole of the final deflection of the electrocardiogram. It is commonly a single wave whose first limb is irregularly convex toward its base; that is, it does not follow the arc of a circle, and often shows a more or less straight portion.

The term diphasic has been commonly applied to certain peculiar forms of the T wave, but there has not been general agreement as to what this term should imply. In general, a movement is said to be diphasic when it has a positive and a negative phase, or vice versa, in reference to any given point. It makes a difference, then, whether we consider the deflections of T in relation to the zero level of the record or to the beginning of T itself, i.e., the S-T junction, which might be at zero, or above or below it. Since electrocardiographic deflections usually are considered as upward or downward in relation to the zero level of the record, it seems best to relate the T wave to this level, also. If there is an apex above the zero level and also one below it, the wave may be

described as diphasic, and the signs + and – may be used to indicate the order of occurrence of the upward (+) and downward (–) peaks; that is, + – or – +. Occasionally a T wave may be found which shows as many as three apices; such a wave might be called triphasic. The term diphasic, however, will be applicable to waves of such varied forms that it does not afford a description of T which would be satisfactory in sorting out waves of similar appearance.

Since further detail in description is desirable, it is recommended that the use of this term be amplified as described below. Having noted the position of the S-T junction as + or – or isoelectric, we must next indicate the number of apices shown by the T wave, using the terms monophasic, diphasic, or triphasic. We must now describe the character of the curve between the S-T junction and the first apex of the T wave. It may be concave toward zero, horizontal, or convex toward zero, and may occasionally leave zero at an angle in a quite straight line. If the line is at first horizontal it always changes to a curve before reaching the apex, and the direction of the curve is determined by that of the peak, so that this curve need not be especially described. The first peak of T should be described as + or –, and measured in millimeters. If no peak appears, T should be described as isoelectric. If there are more than one apex, they should be spoken of as Ta, Tb, and Tc, and their relation to zero indicated as + or – so many millimeters. The curve following the first apex of T need not be described, for it is so dependent for its form upon the position of the different apices in relation to zero and to the beginning of T that it follows from a description of these points.

The description of the T wave will then comprise the following:

S-T junction: deflection +, 0, or –, in mm.

T wave: isoelectric, monophasic, diphasic, triphasic.

$$\text{Course: toward first apex of T} \begin{cases} \text{horizontal} \\ \text{concave (toward zero)} \\ \text{convex (toward zero)} \\ \text{straight} \end{cases}$$

$$\text{Apices: T, or } \begin{matrix} \text{Ta} \\ \text{Tb} \\ \text{Tc} \end{matrix} \text{ (deflection +, 0, or –, in mm.)}$$

For example, T_1 of Fig. 1 would be described as follows: S-T junction –1 mm., T monophasic, course convex, –4 mm. T_3 of this figure would be described as S-T junction +1 mm., T monophasic, course convex, +4 mm. The T wave of Fig. 4*D* would be described as S-T junction +0.5 mm., T diphasic, course concave, Ta = +0.5 mm., Tb = –0.5 mm.

There are records in which it is difficult to mark the ending of T and in which this wave may appear to be prolonged and diphasic or triphasic. This is usually caused by fusion with U, and this fact can be recognized if the duration of T is measured in another lead in which T shows a more definite termination. If this measurement of duration be applied to the doubtful lead, it will be seen that what was thought

to be the prolongation or the final apex of T has really occurred after the end of this deflection, and is therefore either the beginning of U or the peak of U.

The P wave may be described in a manner analogous to that proposed for T. It may be directed upward or downward, may be diphasic or isoelectric, and may show notching of one of its limbs or of the peak. Its description and measurement should follow the general lines suggested for T.

SUMMARY

In view of the present confusion regarding the terms to be applied to the peaks of the electrocardiogram, the usage of Einthoven and of Lewis has been reviewed in the hope of finding a reasonable solution. Lewis' modification of Einthoven's terminology is recommended.

Suggestions are made for naming the peaks of certain types of QRS not particularly mentioned by Lewis, namely, the M complex, the vibratory QRS, and the solely downward deflection.

A method of describing notching and slurring of QRS is outlined, and certain features of the measurement of the duration of P, QRS, and Q-T are emphasized.

A definition of the term diphasic is suggested, to be applied to the P and T waves; also, a method of describing these waves which is considered adequate for statistical grouping is presented.

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THE USE OF THE CATHODE RAY* FOR RECORDING HEART SOUNDS AND VIBRATIONS

I. Studies on the Normal Heart

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THE mechanism of production of the heart sounds and conditions influencing their character have interested physiologists and clinicians for many years. During that time numerous and various instruments were devised for recording them, and a great many observations on the heart sounds were made. A thorough review of the historical developments in this field has been presented by Bierring and his co-workers[1] and need not be repeated here. Many of the instruments more recently developed[2-11] for the graphic registration of the heart sounds embody a string galvanometer as the recorder, and use microphones and amplifiers of various design; some utilize other electrical or mechanical devices for recording the sounds. Observations made with these instruments have yielded valuable information concerning the heart sounds, especially as regards the time of their occurrence in the cardiac cycle, as well as some factors in their production, and the time and duration of murmurs.

Clinicians have long been aware that certain fundamental changes in the heart tones, irrespective of adventitious sounds that are difficult to interpret, may appear in various kinds of heart disease and in other derangements of the circulatory system. It would seem advantageous, therefore, to record all of the vibrations, whether audible or inaudible, which are set up by the heartbeat, so that finer changes in the fundamental heart sounds, as well as the time and character of adventitious sounds, might be detected and studied.

PHYSICAL CONSIDERATIONS

Any vibrating object transmits its movement to the media within which it rests. This movement may be picked up and recorded by mechanical means, or by the ear. Vibrations may be of many types. They may be discerned by the ear if their frequency is sufficient, or they may not be acoustically recognized at all. There are two factors in the thresholds of hearing. One is the energy threshold, which an audible vibration must exceed to be heard, and the other is the frequency threshold, below which a continuous vibration will not be heard.

Vibrations with a frequency and intensity that enable them to be heard are sound stimuli. A musical sound is made up of a fundamental, or basic, frequency, together with a number of higher vibration frequencies which are

*The cathode-ray "vibrocardiograph" was built by the Burdick Corporation.

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called harmonics. Continuous vibrations of sufficiently low frequency will not be heard, regardless of volume or energy level, and vibrations of a frequency in the audible range must reach a certain intensity in order to be heard. The usual heart sound does not have a musical pitch and is essentially a noise. It is made up of a group of different, continuously changing fundamentals and inharmonic partials. Because of these characteristics, a heart sound is often hard to describe satisfactorily.

The ordinary stethoscope, as a medium for picking up heart sounds, has certain disadvantages. A consideration of the character of the sounds heard through the stethoscope involves dealing extensively with acoustics; the stethoscope does not transmit to the ear all of the frequencies of the heart sounds in undistorted form. For example, in a stethoscope in which a column of air is the transmitting medium, the column, once set in motion, may continue to move, thus introducing vibrations to the ear which have not been produced by the heart. In such an apparatus there is no means of preventing this action.

DESCRIPTION OF CATHODE-RAY "VIBROCARDIOGRAPH"

Since it seems possible that information may be gained by recording vibration frequencies lower than those of the acoustic spectrum, an instrument was designed to obtain high fidelity of reproduction of the vibrations produced by the beating heart, rather than to select or emphasize those which are appreciated acoustically. In order to attain this result, air transmission in any form was avoided. In making a record, a water-filled capsule, three inches in diameter and a quarter of an inch in thickness, whose two flat surfaces consist of thin rubber membrane, is placed on the chest, and the pickup unit is firmly strapped in contact with the outer surface of the capsule. The spring spider supporting the button of the pickup is thus kept under strain, and the vibration frequency of the system is correspondingly increased. A specially constructed, dynamic type microphone, with an extremely light moving unit, is used as the pickup. Currents from this pass to an amplifier, and, from the output of the amplifier, connections are made to the vertical or Y-plates of two cathode-ray tubes. One of these, which has a five-inch, long-persistence screen, is used as a viewing tube; the other, which has a three-inch, short-persistence screen, is enclosed in a lighttight housing and is used for photographing the vibrations on 35 mm. bromide paper. Time is recorded on the bromide paper by a small gas tube, flashed by an electric clock motor at the rate of five times a second. In the case of the viewing tube, a tripping device moves the spot across the tube face at a rate which may be synchronized with the heartbeat. By employing the two cathode-ray tubes in this manner, it is possible to watch spot movements on the viewing tube as long as one wishes, and to take records only when desired.

Studies were made to ascertain the fidelity of response of the amplifier and pickup unit. Using a beat frequency oscillator, sine waves were applied to the amplifier. This was found to have a drop off in transmission of less than 2 per cent between five cycles and fifteen hundred cycles per second. In testing the frequency response of the microphone, the pickup unit, without the water capsule, or with the capsule in firm contact, was activated by tuning forks of various frequencies. At frequencies of 50 to 500 d.v. per second, no obvious irregularity of response was introduced (Fig. 1 *A, B, C, D*). The free period of the microphone button, with the unit held inverted and free in air and then gently tapped, was, for two units of slightly different design, 175 and 190, respectively (Fig. 1 *E* and *F*). When the microphone unit was held in firm contact with one surface of the capsule, and the lower surface of the capsule left free, tapping the unit or the water capsule then caused irregular oscillations with various obvious component fre-

quencies (Fig. 1 *G*). This merely indicates the necessity of having the capsule filled with water (containing no air bubbles) and in firm contact with the chest on the one side and the microphone unit on the other. Under these conditions there is no such random movement of the water in the capsule.

Since satisfactory synchronization of sound records and electrocardiograms depends upon adequately controlled time signals, the same circuit was used to activate flashing lamps for the two records simultaneously. To check against possible error caused by parallax, in the case of the sound records part of the voltage acting on the flashing tube was led through small condensers to the amplifier circuit, making sharp breaks in the record with each tube discharge. It is to be seen that there is no significant parallax error (Fig. 1 *H*). Similar precautions were taken in the case of the electrocardiographic records.

It is our belief that, at the paper speed used (97.5 mm. per second), the instrument is more than adequate to record frequencies which can be recognized as discrete waves over a range of 5 to ca. 250 per second. It seems probable that it is adequate to record, with little or no distortion, such higher frequency components produced by the beating heart which contribute to the acoustic qualities observed with the usual stethophones.

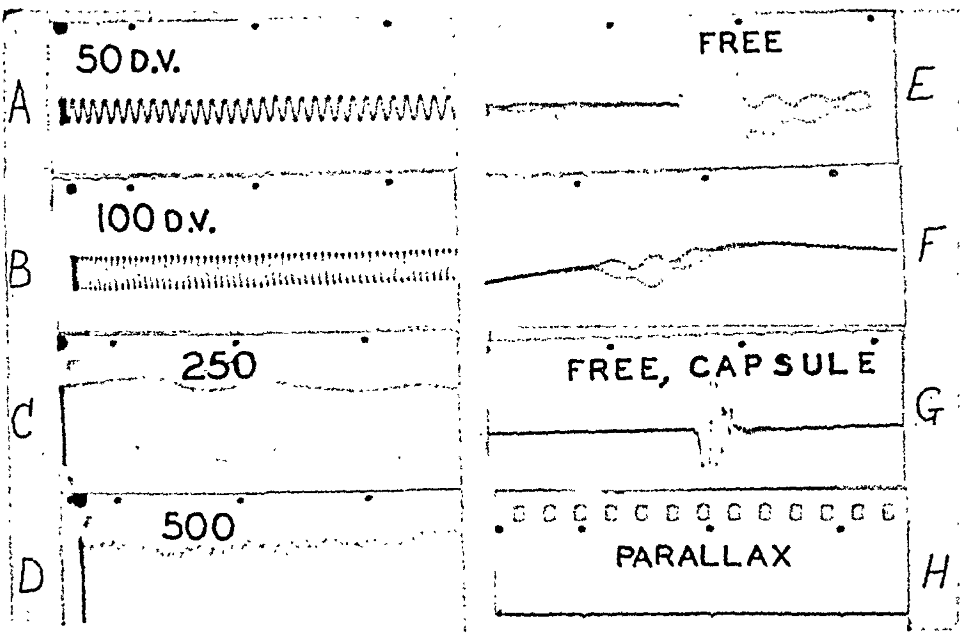

Fig. 1.—*A*, *B*, *C*, and *D* illustrate the response of the amplifier and cathode ray, when applied to a beat frequency oscillator, at 50, 100, 250, and 500 cycles per second. *E*, *F*, and *G* show the response of the microphone to gentle tapping with and without water capsule (see text). *H*, Record testing parallax in the time signalling device.

To record the cardiac vibrations the patient is placed in a recumbent position with his arms at his sides. The microphone is placed over the heart. Tracings from the aortic, tricuspid, mitral, and pulmonic areas are usually made. Because of the fact that the most intense vibrations may be inaudible because of low frequency at a given point, it is often desirable to place the microphone in several positions on the chest wall in order to find the point of greatest vibration intensity, as noted on the fluorescent screen of the viewing tube. Additional records may be made from any other point desired. Each patient was cautioned not to speak, cough, or move during the recording, and care was taken to induce patients to relax. In this way, the introduction of artifacts into the curves was avoided. In accord-

ance with standard practice, electrocardiograms (Lead II) were taken simultaneously with the vibrocardiograms, with which they were synchronized by means of the lighting mechanism described above.

CHARACTERISTICS OF CARDIAC VIBRATIONS

Many different types of curves have been obtained from normal and abnormal hearts. A cursory analysis (true analysis of curves of this sort requires considerable mathematical calculation which will not be included here) shows that there are many differences in the vibrations. Variations in frequency, frequency rate, amplitude, and conformity of the curves were noted.

The wave shape of the vibrations from the normal and diseased heart, as shown by the vibrocardiograph, is a graphic summation of all of the waves which are present. If the apparent frequency is changing in a given "heart sound," we know that either inharmonic partials are present or a new frequency is being generated; that is, if a new wave is being generated, it may effect a complete change in frequency and shape of the wave under observation. If higher harmonic or inharmonic waves of sufficient amplitude are present, they may appear as more or less obvious, small wavelets, superimposed on the large fundamental waves.

In this communication we shall confine ourselves to a brief discussion of normal cardiac vibrations. Figs. 2, 3, 4, and 5 are typical examples of curves obtained from subjects who had no demonstrable cardiac, pulmonary, or bony thoracic abnormalities.

Conformity of Waves and Time of Their Occurrence in the Cardiac Cycle.—The appearance of the wave complexes varies with the point on the chest from which they are recorded. The first and second wave groups (representing the first and second "heart sounds") are easily identified by the longer duration and sharper spiking of the second wave complexes, and by correlating the time of their occurrence with the electrocardiogram. The first sound complex begins with one or two waves of a smooth character which fall between the crest of the P wave and the upswing of the R wave of the electrocardiogram. These waves occur during auricular systole, but are of a frequency (below forty cycles a second) too low to be heard. A sudden upward or downward movement of the cathode-ray record falls before, or near, the peak of R, and represents the onset of the audible portion of the first heart sound. Thereafter comes a series of gross waves of irregular character, varying from three to six in number, and often punctuated by a series of small, sharp points which represent the interpolation of many wavelets of higher frequency. Depending on the number of deflections in the group representing the first disturbance, the complex may extend well through the R-T interval.

The second group of deflections begins and ends more abruptly than the first. In records taken by this method, the onset of the second com-

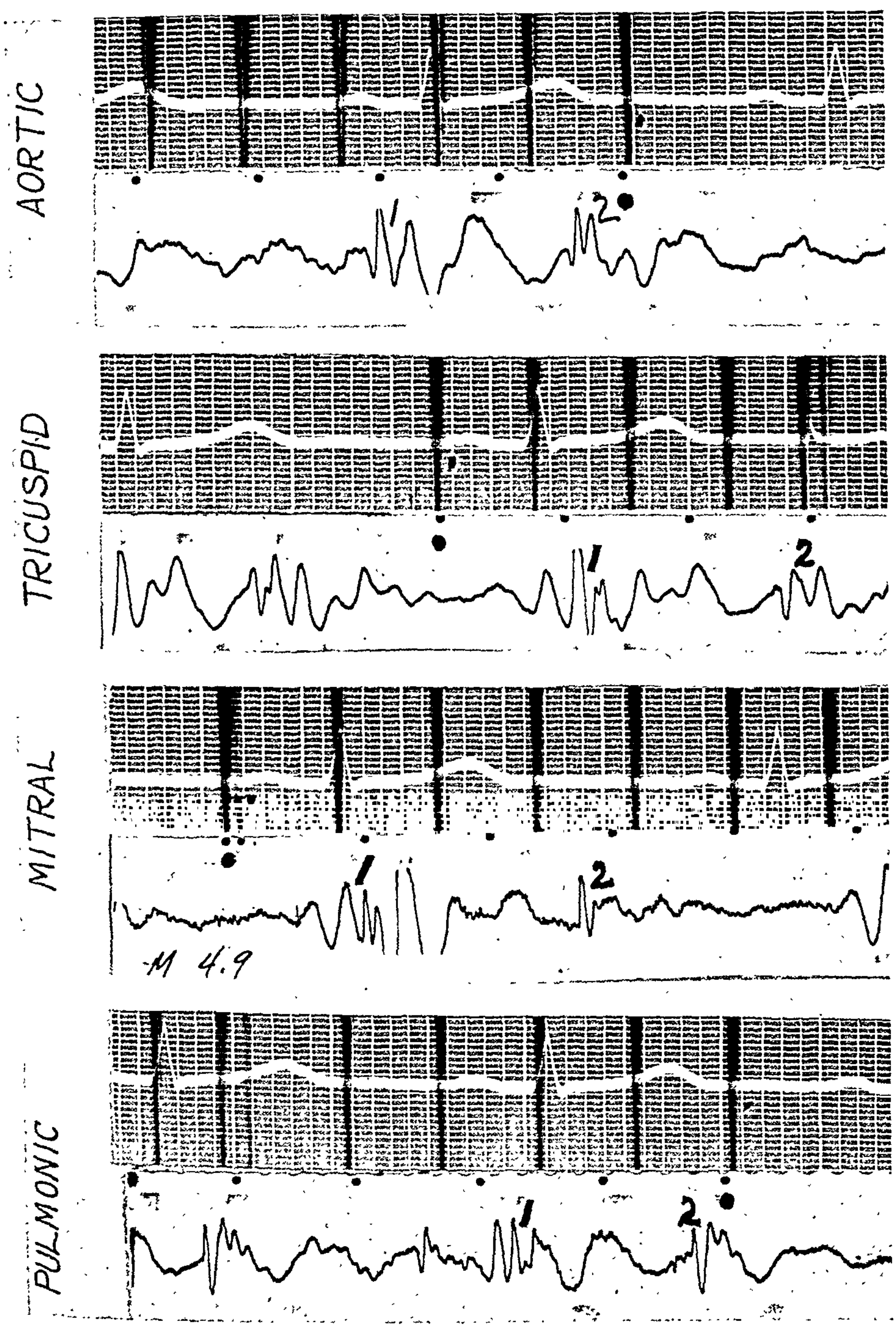

Fig. 2.—W. P., white man, aged 40 years. Sthenic habitus; no cardiac or pulmonary abnormalities; heart tones of "normal quality" at all auscultation areas; no adventitious sounds. The first and second heart sound complexes are designated *1* and *2* on the record.

The electrocardiographic and stethographic tracings were recorded on separate instruments at slightly different paper speeds. Synchronization was accomplished by the use of two flashing lamps, marking fifths of seconds on each of the two records simultaneously. Occasional interruption of the signal circuit indicates a corresponding instant in the two records. From the first flash of the lamps following such an interruption, the events in each tracing may be accurately measured. An ink dot is placed at one signal on each record to indicate that these are synchronous points. In some instances, irregularities of the flash interval follow a period of interruption; these should not be mistaken for irregularities in paper speed.

plex lies on the descending limb of the T wave—usually on the latter part of the wave.

It is interesting that, in most cases, a well-defined wave occurs in early diastole; this corresponds to the point occupied by the normal third

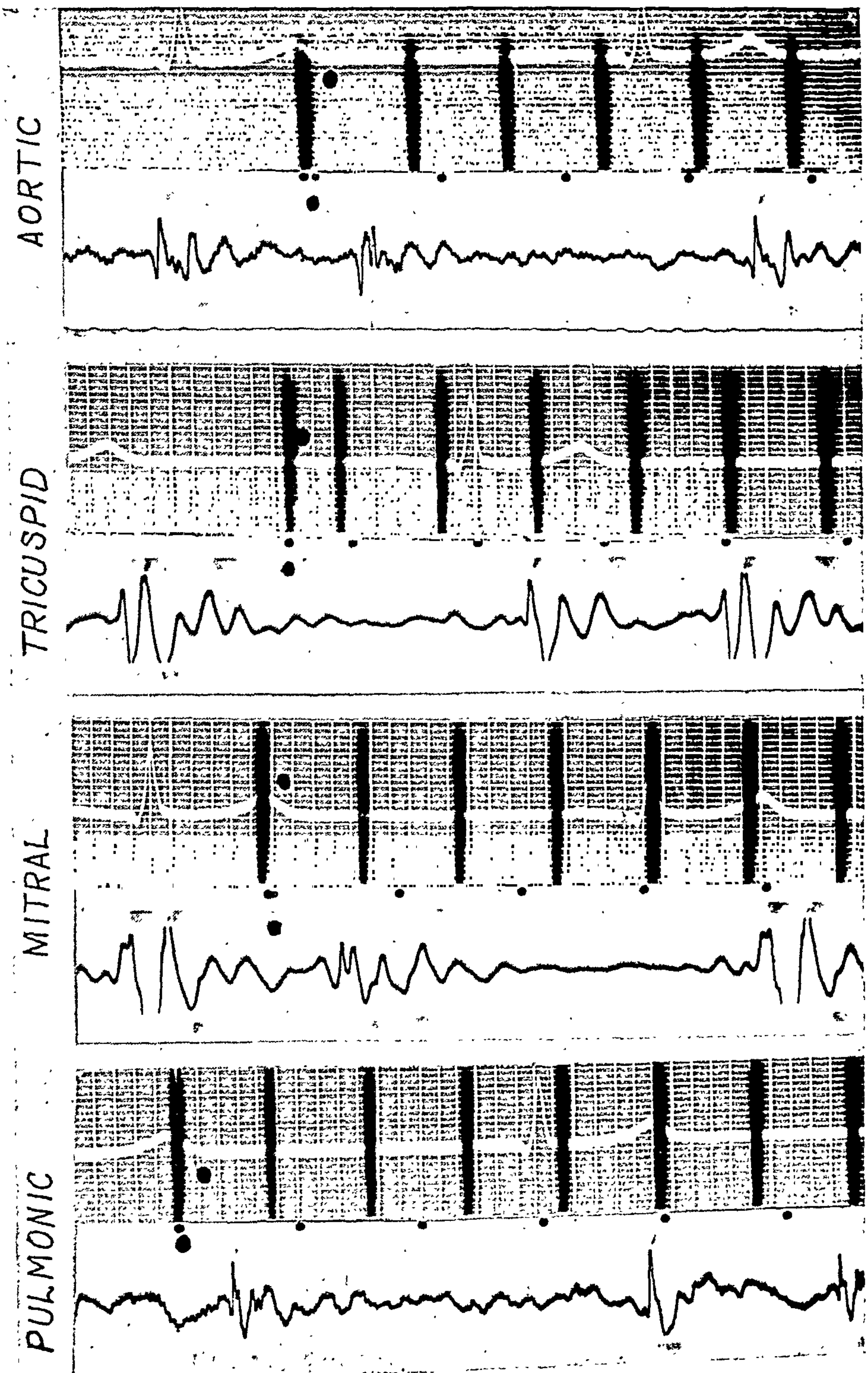

Fig. 3.—J. G., white man, aged 24 years. No history of cardiac or pulmonary disease.. Sthenic habitus; heart not enlarged. Normal heart sounds at all auscultation areas, although there is close splitting of second sounds at the pulmonic and aortic areas. Aortic second equals pulmonic second sound.

heart sound, although no third sound may be heard on auscultation. This wave is usually of low frequency and of no acoustic value. When such a wave is clearly present in the tracing from one auscultation area, it may generally be detected in any of the other three areas. McKee[12] noted, in studying stethographic tracings from 100 normal children, that four heart sounds were usually present; that is, in addition to the

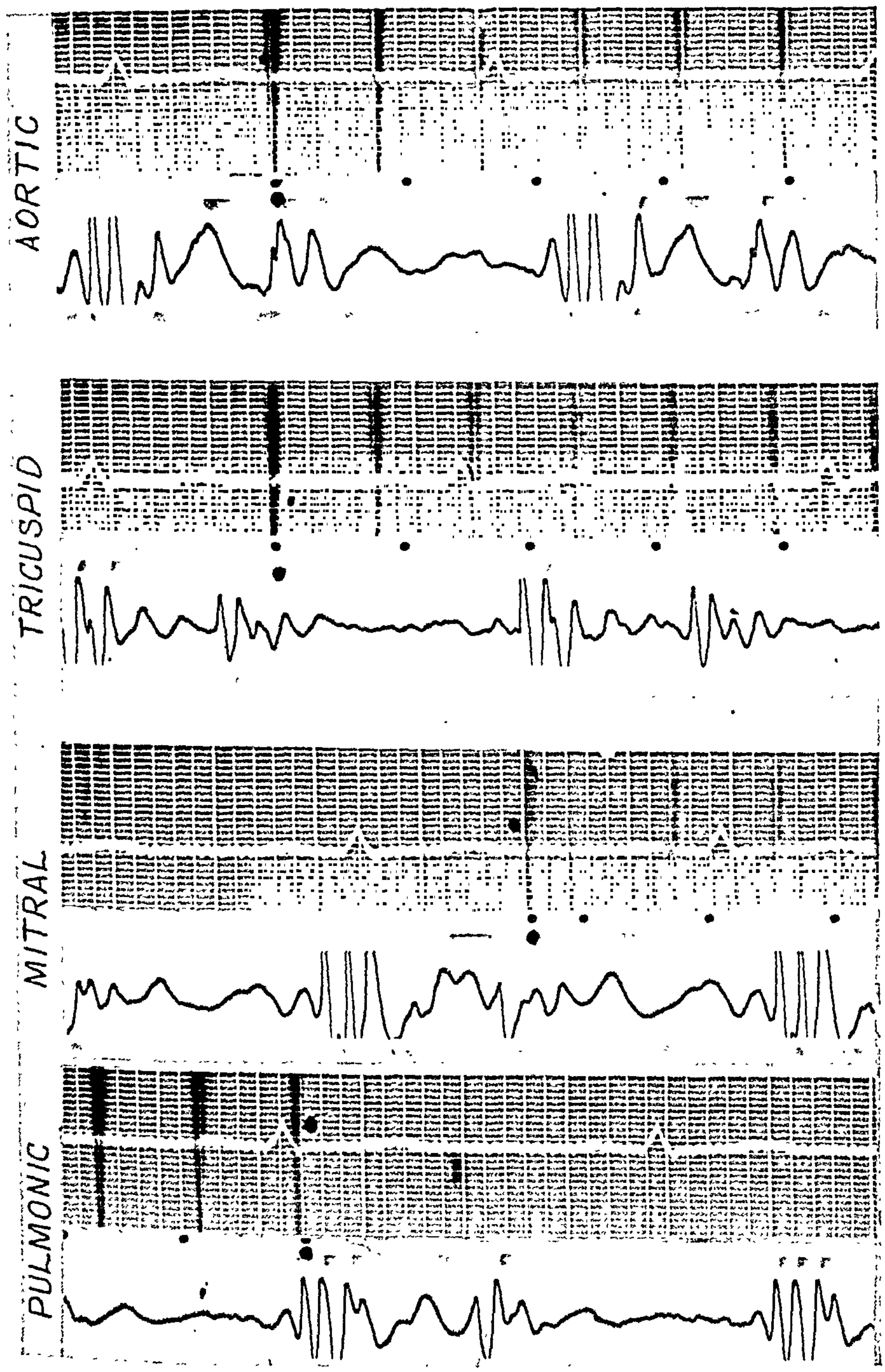

Fig. 4.—M. S., white man, aged 38 years. No history or physical signs of heart disease Hypersthenic habitus. The sounds are of "good quality" at all areas.

first and second sounds, a physiologic third sound wave occurred early in diastole, and a fourth sound wave, supposedly auricular in origin, preceded the first sound waves. In her series, 69 per cent of the tracings showed a third heart sound complex, and 94 per cent showed a presystolic sound. The "third" and "fourth" sound wave groups may

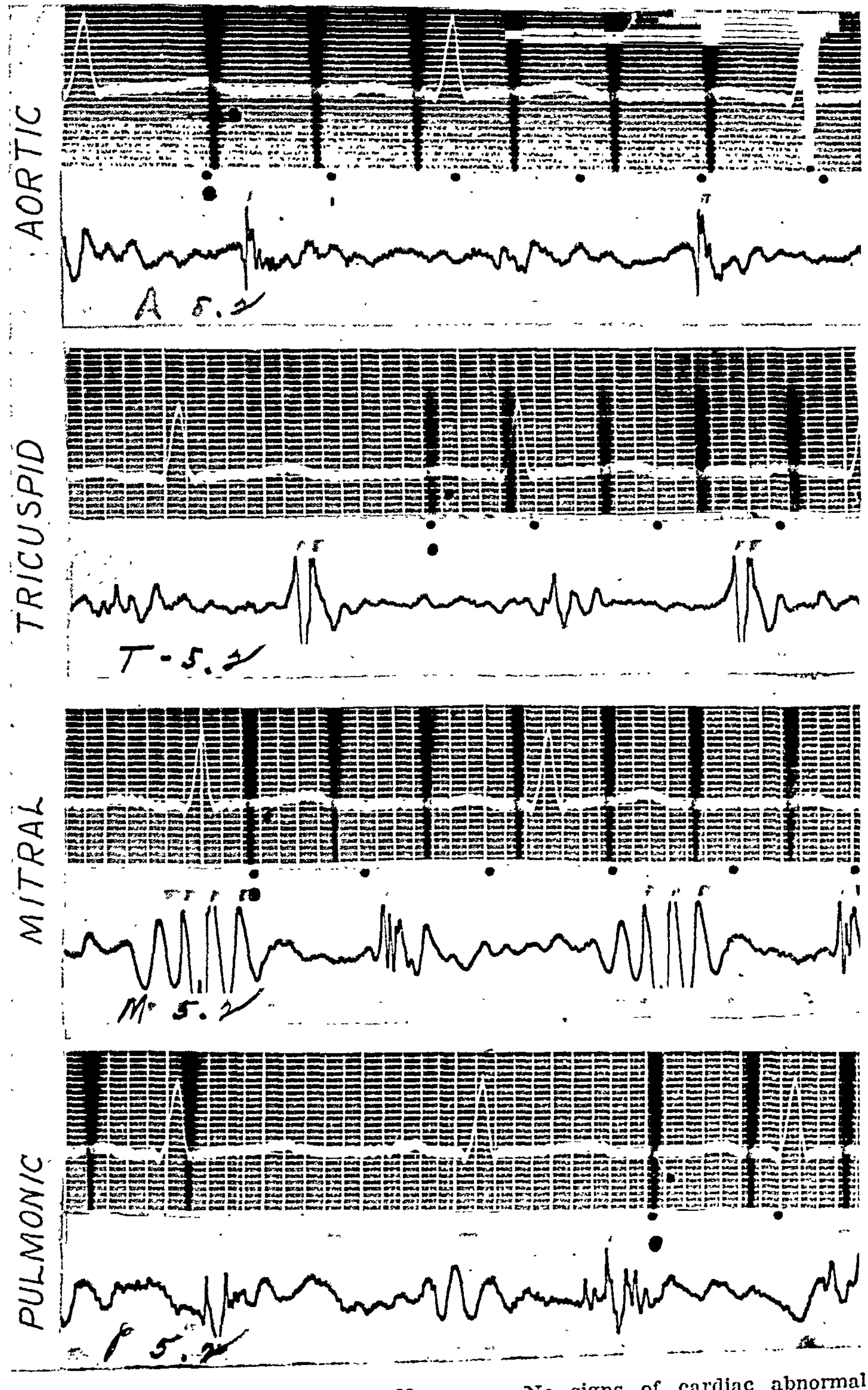

Fig. 5.—J. T., white man, aged 23 years. No signs of cardiac abnormality. Hypostheniç habitus. The heart sounds are of normal character at all areas. Note pronounced "auricular" waves in mitral area tracing.

be recognized in most of our records as well-defined waves of low frequency (below auditory level).

Duration of Vibrations.—The duration of the vibration complexes likewise varies with the area of the precordium from which the curve is recorded. At the aortic, tricuspid, mitral, and pulmonic areas, the first wave complex extends over a period ranging from 0.14 to 0.24 second. The presystolic waves which occur during the P-R interval, although they are of low frequency and without acoustic significance, must be considered a part of the disturbance incident to the atrial and presphygmic phases of the heart cycle. Therefore, these measurements include the envelopes which occur between the P wave and the point where they disappear, during the R-T interval, and comprise the "first wave complex." As a rule, the "second wave complex" is of shorter duration; it varies from 0.02 to 0.16 second. It should be emphasized that the first (audible) sound is, of course, normally of much shorter duration than the vibration complex described above, and that the vibration complexes are reflections of vibrations arising within the heart and of movements of the heart itself which are imparted to the chest wall during the cardiac cycle.

The instruments that have been previously devised for graphic registration of the heart sounds have usually been constructed so that sufficient distortion is introduced into the curves to minimize adventitious sounds or to emphasize various audible frequencies. This may only be accomplished, however, by sacrificing lower frequencies which, in themselves, may be inaudible or ill defined, but, when summated with other waves, help to establish the character of the sound. Furthermore, only a small segment of the disturbance is recorded, so that its exact relation to the cardiac cycle may not be well defined. The onset of the first sound has been located, by various observers, using different instruments, at the peak of the R wave or on the ascending or descending limb of the R wave. The use of the cathode-ray unit with these transmission characteristics shows, however, that the first heart sound complex begins during auricular systole; the character of these waves, as regards number and frequency, may possibly modify the audible qualities of the first sound. Such records may be of distinct advantage in detecting cardiac abnormalities that might otherwise be missed.

SUMMARY

An instrument which embodies a special dynamic microphone, amplifiers, and cathode-ray tubes, whereby vibrations set up by the heartbeat may be recorded, is described. Two cathode-ray tubes are employed; one is used to photograph the vibration complexes on a moving film, and the other, which has a long-persistence screen, is used as a viewing

tube. Curves obtained from normal hearts are presented. Certain advantages which this instrument seems to have over other stethographic devices are discussed.

The authors wish to express their appreciation to Lida W. Smith for financial assistance in this work.

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A MORPHOLOGIC STUDY OF THE CARDIAC CONDUCTION SYSTEM IN UNGULATES, DOG, AND MAN

PART II: THE PURKINJE SYSTEM

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JOHANNES Evangelista Purkinje died in 1869. It is unfortunate that he could not have realized the important role which the Purkinje cells were to play in the development of modern cardiology. These peculiar muscle elements were first seen by Purkinje in sheep hearts, and described by his pupil, Palicki,[1] in 1839, and by himself[2] in 1845. They constitute a distinct type of muscle tissue (Fig. 1*A*) which can readily be distinguished from other myocardial elements. The cells occur in rows, two to five of which form a strand (Fig. 2*B*). The cells are short, thick cylinders, with distinct outlines (average diameter, 30 to 60 microns). The cytoplasm is slightly basophilic, the fibrils are irregularly arranged, and cross striations are rare and indistinct (Fig. 1*B*). The cells are characteristically binucleated (Fig. 2*A*). The nuclei lie at or near the clearer center of the cell; they are oval; their long axes often run transversely; and they contain a moderate amount of chromatin. Occasionally, only one nucleus is seen; less frequently, there are more than two. The cells are practically identical in structure and arrangement, wherever they are found. However, when the strands are compressed between muscle bands, they appear thinner and longer.

We have studied the Purkinje system in fifteen bovine, seventeen ovine, three equine, and five porcine hearts. Critical study of homologous areas in thirty-six human and seventeen canine hearts has led us to conclude that the structure of the so-called sinoventricular conduction system in these forms differs radically from that in the ungulate heart.

THE ORTHODOX VIEW OF CARDIAC CONDUCTION

According to the view held by most cardiologists and physiologists, the cardiac impulse is transmitted from the right auricle to the ventricles and spreads out over the inner myocardial surfaces of the ventricles through the Purkinje system. Most experimental cardiologists also hold that the secondary and tertiary impulse centers are found only in Purkinje elements. This conception of the conduction system of the heart developed from the work of Tawara,[3] Moenckeberg,[4] Lewis,[5] Mahaim,[6] Yater,[7] and others. It is essentially as follows:

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The Purkinje system is present in all higher animals (also in birds—Drennan[8]). In man and dog, as well as in other animals, it begins as ordinary or special auricular muscle fibers in the right auricular wall, in front of, below, and above, the coronary sinus. These auricular fibers run toward the central fibrous body, near which they change into a special type of muscle which forms the node of Tawara. The anterior fibers of the node run into the connective tissue of the central fibrous body, and become the essential constituent of the His bundle.

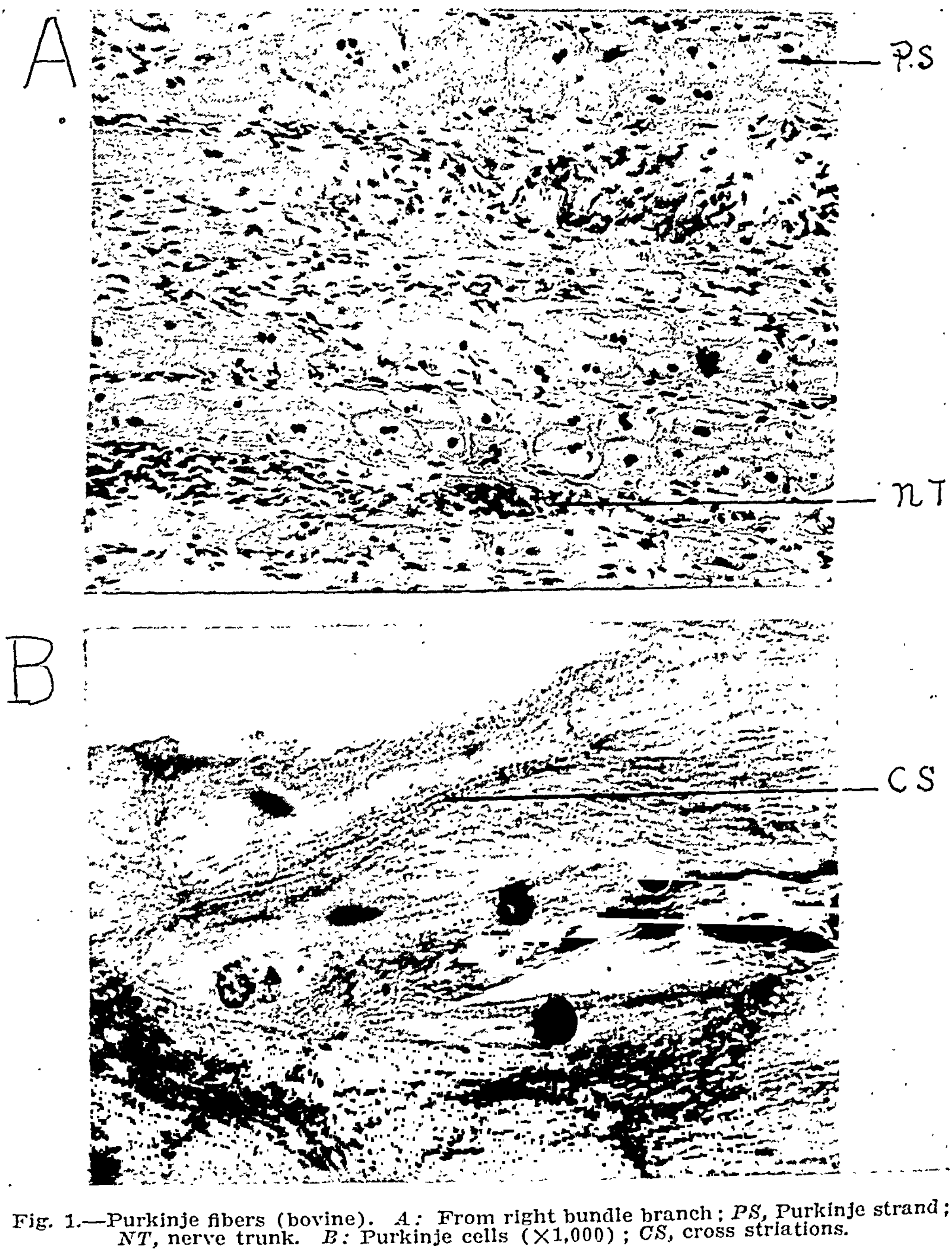


Fig. 1.—Purkinje fibers (bovine). *A*: From right bundle branch; *PS*, Purkinje strand; *NT*, nerve trunk. *B*: Purkinje cells (×1,000); *CS*, cross striations.

In man and dog, the left branch separates into fasciculi which are given off from the main trunk at different levels. These "soon" be-

come Purkinje fibers, which spread out over the inner surface of the ventricular myocardium. The right branch enters the myocardium below the tricuspid base, and runs within the myocardium to the papillary muscle. In the intramyocardial portion, the fibers of the branch are similar to ordinary myocardial fibers. At the level of the papillary muscle the branch becomes subendocardial, and its fibers change to Purkinje cells which spread out in strands underneath the endocardium.

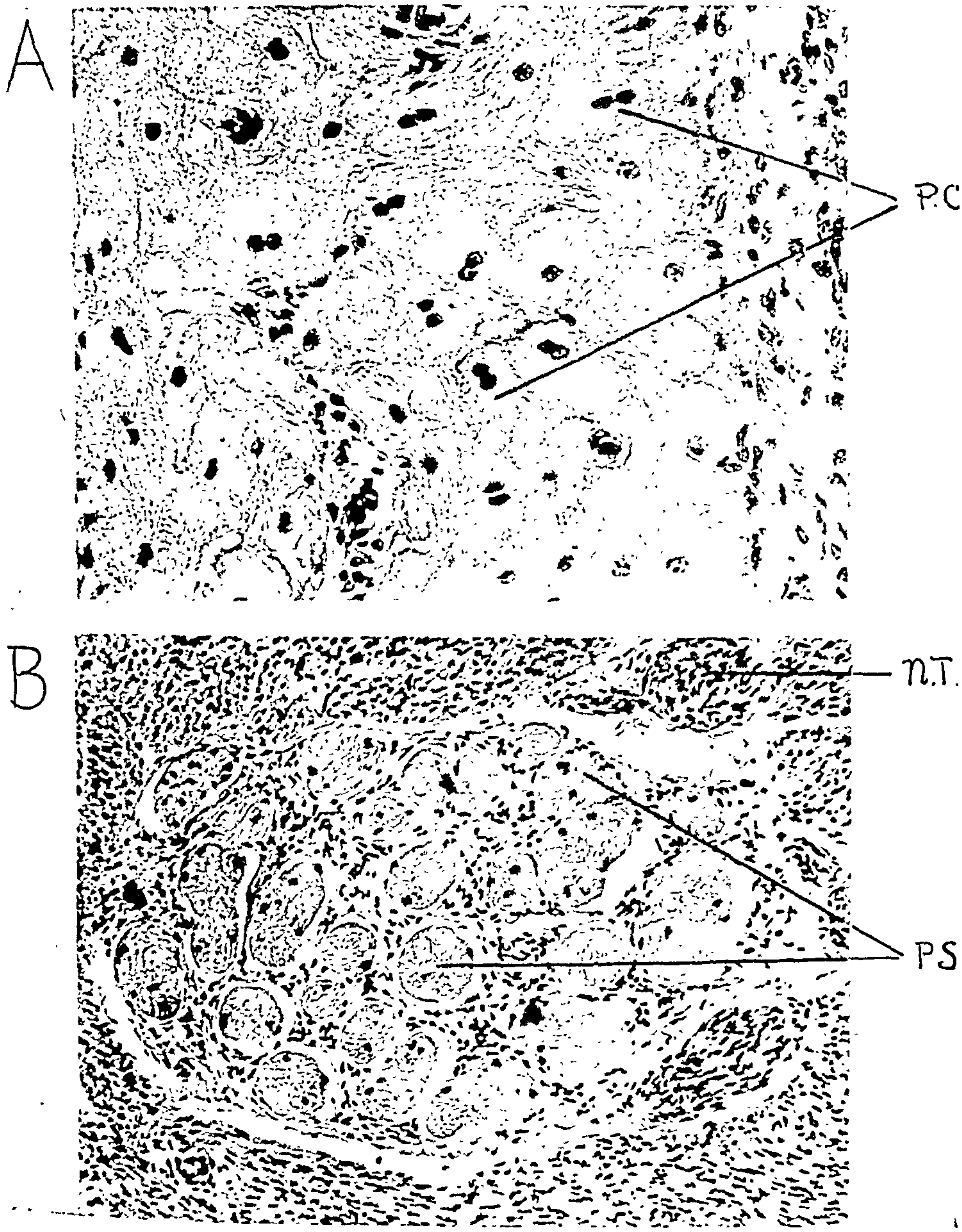


Fig. 2.—Purkinje cells (sheep). *A*: From Purkinje network; *PC*, Purkinje cells. *B*: Cross section of branch in moderator band; *NT*, nerve trunk; PS, Purkinje strands.

In the ungulate the main bundle bifurcates at the lowermost portion of the septum membranaceum, and each branch runs obliquely down-

ward through the myocardium toward the endocardial surface of the heart. The right branch becomes subendocardial at the base of the moderator band; the left, at various distances above the papillary muscles. Secondary branching occurs on both sides of the septum below the point where the branches become subendocardial, and from this branching a subendocardial network is formed. The essential constituent of the main trunk, its branches, and the subendocardial network is the Purkinje cell.

THE PURKINJE SYSTEM IN SHEEP AND CATTLE

In the bovine and ovine hearts which were used for this study, we found no direct muscular connections between the atrial muscle fibers and those of the node of Tawara. The node is best exposed by cutting the attachment of the lateral, right auricular wall to the fibrous auriculoventricular ring, and then severing the attachment of the atrial muscle to the septal base of the tricuspid valve. The atrial wall can then be readily lifted up and to the left, thus exposing the areolar tissue in the auriculoventricular groove. This tissue separates the lower, posterior, right atrial wall from the right, upper, ventricular septum, and, when it is removed, the node of Tawara comes into view.

I. THE NODE OF TAWARA

This muscular nodal tissue has its origin in the posterior right part of the central fibrous body and lies in the areolar tissue at the top of the muscular ventricular septum. In sheep it is usually knob-shaped. In cattle it is, as a rule, fan-shaped (Fig. 3). The "fan" handle forms the attachment to the central fibrous body and the beginning of the bundle. The node is faintly yellow, and its upper surface looks like a heap of matted yarn. Its peripheral tissue sprawls out over the top of the ventricular septum to the right and downward. A prominent strand which forms the upper limit of the node runs backward along the central fibrous ring. The anterior boundary is often made up of another heavy strand which runs downward into the right ventricle. Between these two strands, groups of fibers meander out from the middle of the node. Near the central fibrous body these interlace to form a network; more laterally, they are lost in the fatty tissue of the auriculoventricular groove. Some of the basal fasciculi of the node run forward and become the Purkinje elements of the His bundle.

The histologic structure of the node was accurately and lucidly described by Tawara. The nodal parenchyma consists of a mass of faintly cross-striated, slender muscle fibers, which either interlace or form whorls (Fig. 4*A* and *B*). The diameter of the individual fibers is slightly less than that of the average atrial and ventricular muscle element, and the fibers seem to possess more nuclei. These are usually rod-shaped or oval. In the whorls, diplonuclei, characteristic of Purkinje cells, are seen. The meshes of the reticula vary in shape and in

size. They are largest in the peripheral part of the node. The strands that make up a reticulum are composed of many layers of closely packed cells. The reticulated arrangement is most marked in the strand of nodal tissue which extends into the ventricle. The whorls are most numerous in the upper strand. In the whorls, cell outlines are fre-

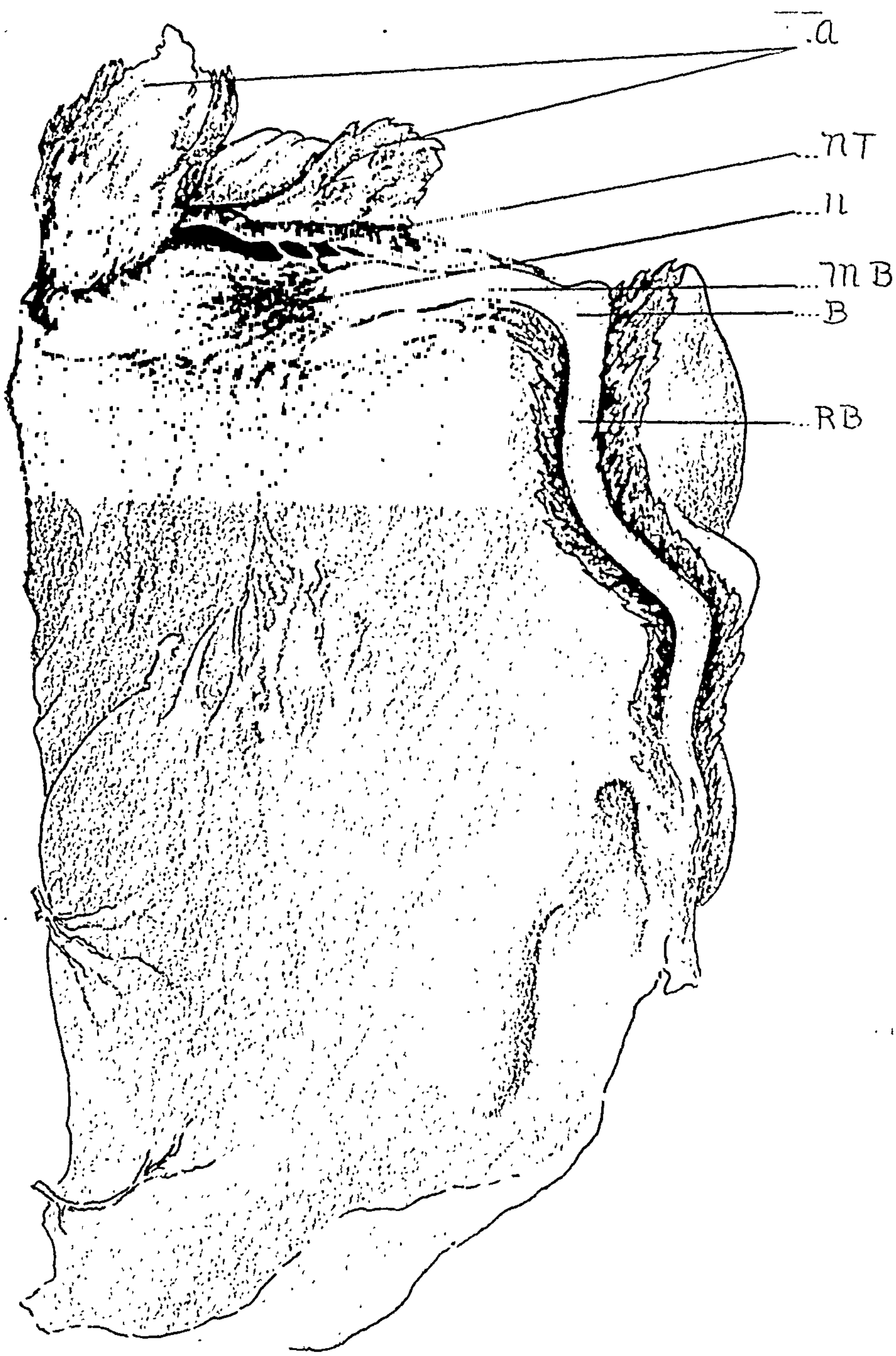


Fig. 3.—The His bundle (bovine). *A*, Auricular wall (turned back); *NT*, nerve trunk; *N*, node of Tawara; *MB*, main bundle; *B*, bifurcation; *RB*, right branch.

quently absent. We have never observed vessels larger than arterioles, and capillaries are scarce. Nerve elements are present near the His bundle and also in the peripheral part of the node. The meshes of the reticula are filled with loose, connective tissue.

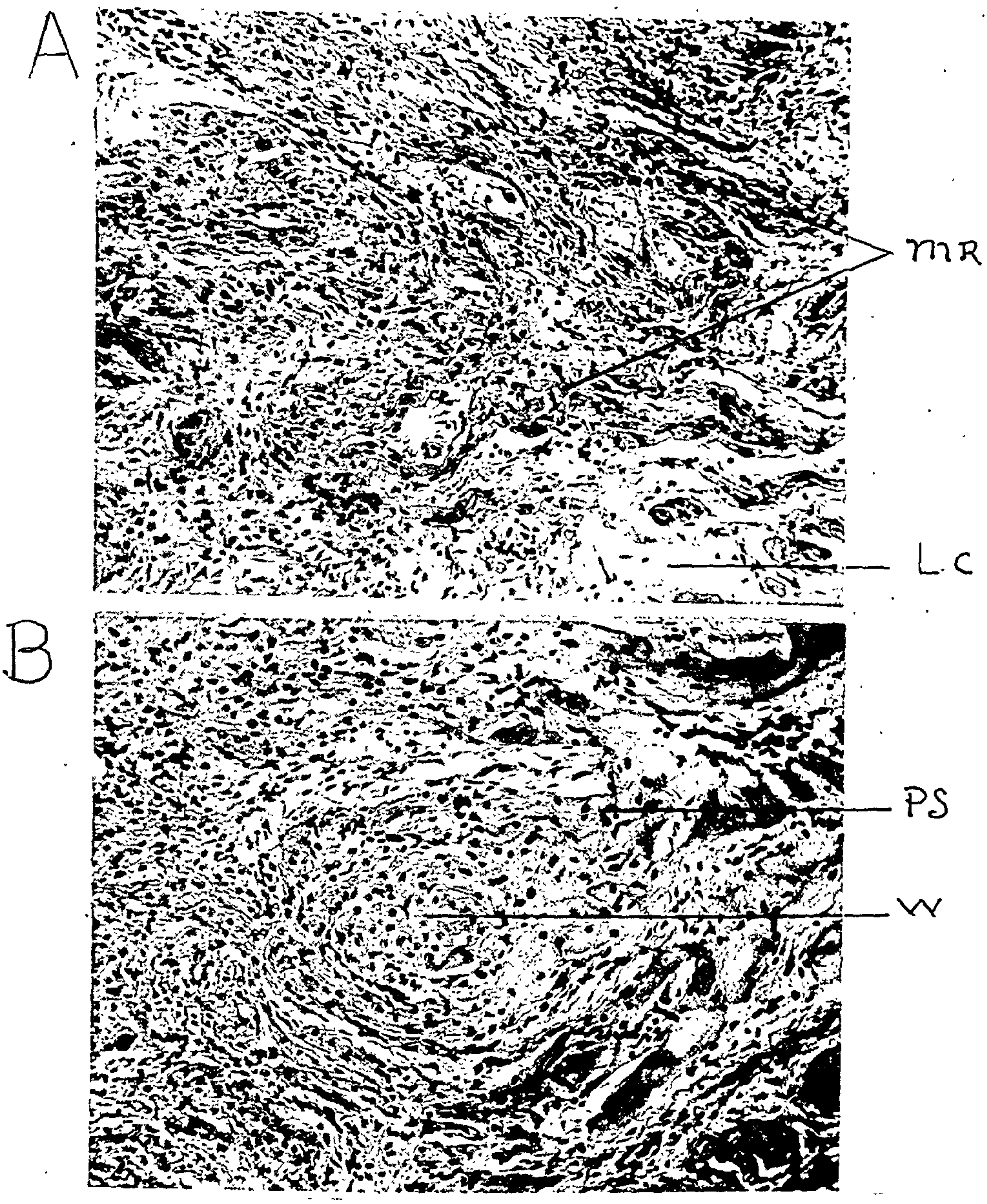


Fig. 4.—The node of Tawara (sheep). *A: MR*, muscular reticulum; *LC*, loose connective tissue. *B:* Beginning of His bundle; *PS*, Purkinje strands; *W*, whorl.

II. THE HIS BUNDLE AND PURKINJE NETWORK

A: Gross Description

In sheep and cattle the His bundle and the Purkinje network are practically identical except as to size. The trunk, beginning to the right of the central fibrous body, runs forward and downward at the top of the muscular ventricular septum. At the lowest part of the fibrous septum, it divides into a right and a left branch. These make their

way through the myocardium obliquely, to the endocardium of their respective ventricles. The branches reach the inner lining of the heart just above the moderator band on the right side, and at various distances above the papillary muscles on the left. Secondary branching takes place on both sides as the endocardium is reached. On the right side small branches are given off at the base of the moderator band. The main branch, however, continues forward in the band, giving off numerous twigs within it, and, as the remainder of the branch reaches the anterior wall of the ventricle, it breaks up into numerous smaller twigs. The secondary branches form the right Purkinje network. On the left side, the branch forks, one limb going to the anterior, and the other to the posterior, papillary muscle. In the crotch between the limbs many small twigs are given off. By further subdivision of limbs and twigs the left Purkinje network is formed. The subendocardial Purkinje network can be seen with the naked eye in the hearts of sheep and cattle. And, because the His bundle and the Purkinje network are ensheathed in connective tissue, the space between the connective tissue and the Purkinje elements can be injected with a suspension of colored particles. DeWitt[9] had a beautiful model of the bundle and the Purkinje network constructed in 1909. Lhamon[10] injected the network with India ink, in 1912; Aagaard and Hall,[11] in 1914, and Cardwell and Abrahamson,[12] more recently, made similar injections.

B: Microscopic Description

The main bundle and the Purkinje network are composed of strands of Purkinje fibers and collections of nerve fibers. These are separated by interstitial tissue and surrounded by a sheath of connective tissue. In the upper, anterior part of the node of Tawara, some of its muscle strands change abruptly into characteristic Purkinje cells. These, together with the nerve trunks which join them at this place, form the main part of the His bundle. The Purkinje strands rarely interlace in the bundle but run in a more or less parallel fashion among the nerve trunks. The strands continue through the right and left branches and into the Purkinje network.

It is generally assumed that the Purkinje strands terminate by changing into ordinary ventricular muscle near the endocardial surface, but Hessling,[13] as early as 1854, found Purkinje fibers intramuscularly and subpericardially. Cardwell and Abrahamson followed the Purkinje strands far into the myocardium of both ventricles, and found them just underneath the pericardium and penetrating the entire septum. We found Purkinje strands deep in the muscle of the septum, on the right and left sides, and within a millimeter of the pericardium of both ventricles. Thus, the Purkinje strands form an intramyocardial as well as a subendocardial network. Nowhere did we find any histologic evidence of a change from Purkinje cell to ordinary muscle fiber. Even the thinnest Purkinje strand is separated from the myocardium by connective tissue.

Such, in brief, are the structure and the arrangement of the Purkinje cells in sheep and cattle. These elements constitute only a part of the His-Tawara system. The Purkinje strand is neither the most conspicuous element, nor, perhaps, the most important part of the His bundle. Although Wilson,[14] as early as 1909, accurately described the nerve tissue of the part of the His-Tawara system which he had investigated, it is astounding that investigators of the His bundle should have given such scant consideration to its nerve elements. Attention has been called to the fact that nerve elements occur in the anterior part of the node of Tawara. Numerous nerve trunks and large blood vessels occur in the fascia at the top of the muscular septum, and many ganglion cells and nerves are found in the auriculoventricular groove in the periphery of the node. In the areolar tissue surrounding the main bundle, numerous ganglion cells and nerve fibers occur. In places these form groups containing hundreds of nerve cells (Fig. 5*A*). Wilson observed large collections of these cells at the bifurcation of the bundle; we found them there, and also in the periphery of both main branches (Fig. 5*B*). In the trunk and its right and left branches, nerve fibers occupy more than half of the structure. Nerve fibrils accompany every Purkinje strand.

Thus, there exists in these ungulate hearts a peculiar type of muscle tissue which differs strikingly from that of other cardiac muscle elements, both in structure and arrangement. This tissue is located in the ventricles, appears to originate in the central fibrous body, forms the node of Tawara and the Purkinje strands of the His bundle, and spreads out as a network, not only underneath the endocardium, but also intramuscularly. The bundle also contains numerous nerve fibers and ganglion cells, and nerve fibers accompany the Purkinje strands in the Purkinje network. The entire system is supplied with capillaries, minute arteries, and veins, and is separated by connective tissue from the rest of the heart.

THE PURKINJE SYSTEM IN THE HOG

The Purkinje system in some porcine species is very similar to that in sheep and cattle. In other species, in which the moderator band and the papillary muscles are poorly developed, the Purkinje system is inconspicuous. As a rule, the node lies nearer the tricuspid base than in sheep and cattle. The nodal tissue appears to be plastered to the upper part of the right side of the interventricular septum. In some hearts a band of nodal tissue extends backward to the right of the central fibrous ring. In the hog, as in the other species studied, a conspicuous septal branch of the right coronary artery, which travels subpericardially in the auricular wall toward the central fibrous body, leaves the atrial wall and enters the ventricular septum just posterior to the central fibrous body. This is the artery which has been designated by other observers as the artery of the node. The septal artery followed this course in only 20 to 30 per cent of the hearts which we studied.

The main bundle and the right and left branches, as well as the Purkinje network, are indistinguishable from homologous parts in sheep and cattle. The histologic structure is also nearly identical, except that the interlacing in the nodal part is not so apparent; the nodal musculature simulates the Purkinje cells much more than it does in sheep and cattle, and there is no abrupt change from the nodal cells to those of the bundle. Nerve bundles are more numerous in the hog, and the Purkinje cells are not so uniformly binucleated. An intramyocardial Purkinje network is also present in the hog.

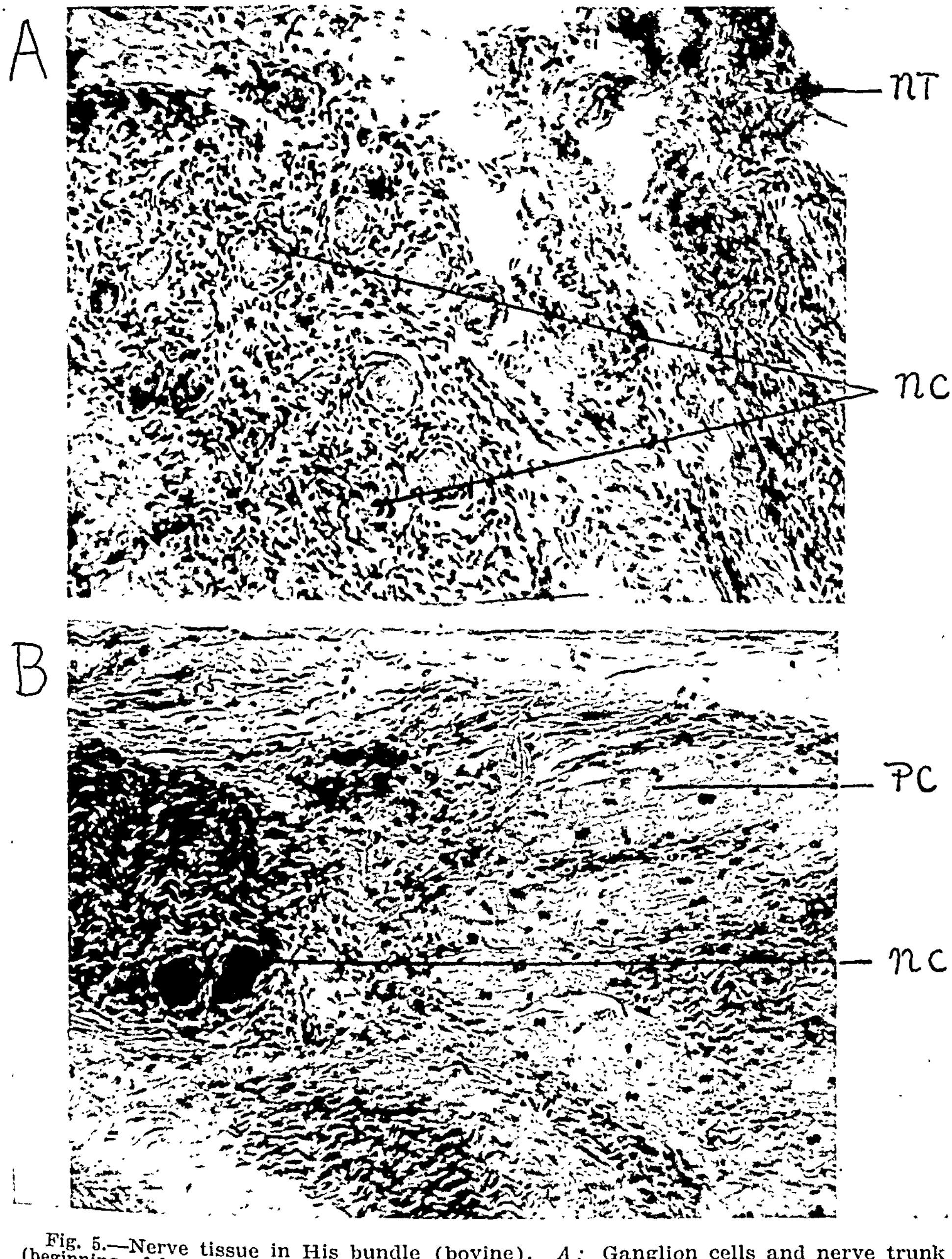


Fig. 5.—Nerve tissue in His bundle (bovine). *A:* Ganglion cells and nerve trunk (beginning of bundle); *NT*, nerve trunk; *NC*, nerve cells. *B:* Large nerve and ganglion cell (right branch); *PC*, Purkinje cells; *NC*, nerve cells.

THE PURKINJE SYSTEM IN THE HORSE

We were surprised to find that neither the node of Tawara nor the main His bundle could be brought to view in the equine heart by our dissection method, but, by removing the endocardium at the base of the small, fibrotic moderator band on the right side, and above the small, fibrotic papillary muscles on the left side, the thin, fibrous, right and left branches could easily be followed upward.

On the right side, the branch enters the myocardium, runs upward one to two millimeters underneath the endocardium, continues under the base of the tricuspid, and finally is lost in a tough fascia at the top of the right side of the ventricular septum in the locality of the septum fibrosum. Numerous bands of ordinary muscle fibers are attached to the branch. When these are picked off, the slender, ribbon-like branch is seen to be about two millimeters in width and less than one-half millimeter in thickness. On the left side, the tiny strands, running from each papillary muscle, unite to form the left branch in the region where the homologous junction occurs in sheep and cattle. The branch plunges into the myocardium, continues obliquely upward through the septum, and, finally, as a slender string about 1 mm. in diameter, enters the left side of the thick fascia, whence, like the right branch, it cannot be traced farther. Numerous muscle fasciculi are also attached to the left branch. Small branches of the ribbon appear to run into the myocardial septum. The left ribbon is wider and thinner than the right.

Histologically, the moderator band and the right branch are composed of fibrous tissue in which a few rows of distorted, misshapen, Purkinje cells are scattered. These appear atrophic. Many of the cells are without nuclei and only rarely is a diplonucleated cell seen. The left branch has the same structure as the right. In the connective tissue one small nerve trunk was seen. In cross sections taken from below the moderator band, a layer of large vacuolated cells, more or less surrounded by typical fat cells, is found subendocardially (Fig. 6*A*). Occasionally, strands of round, slightly basophilic cells, surrounded by a distinct layer of connective tissue, are encountered. These appear to be the Purkinje fibers, although nuclei are scarce. The thick fascia above the attachment of the tricuspid is made up of cellular, fibrous tissue in which are imbedded a single nerve and a few strands of shrunken Purkinje cells similar to those in the right and left branches (Fig. 6*B*). No definite node of Tawara was observed.

The thin ribbons encountered in the equine heart in the region of the right and left branches of the His bundle, and the strands observed in the fascia above the base of the tricuspid valve appear to be the vestigial homologue of the Purkinje system in sheep and cattle.

THE PURKINJE SYSTEM IN MAN

Gross Anatomy

Our experience in two cases of bundle branch block led to our interest in the conduction system of the heart. Post-mortem examination

revealed no significant lesions in the region of the left or right branch in either heart; therefore, we concluded that the proper localities had not been examined and determined to find the His bundle and its main branches by dissection. Since the His bundle is described and illustrated in texts on human anatomy (Spalteholz[15]), dissection of the bundle seemed feasible. When the first four or five dissections resulted in failure, the results were blamed on poor technique, but when the eighth, ninth, and tenth attempts were also unsuccessful, we began to question the statements and illustrations in the texts. By the time the fifteenth dissection of the bundle region in human hearts had been completed, we

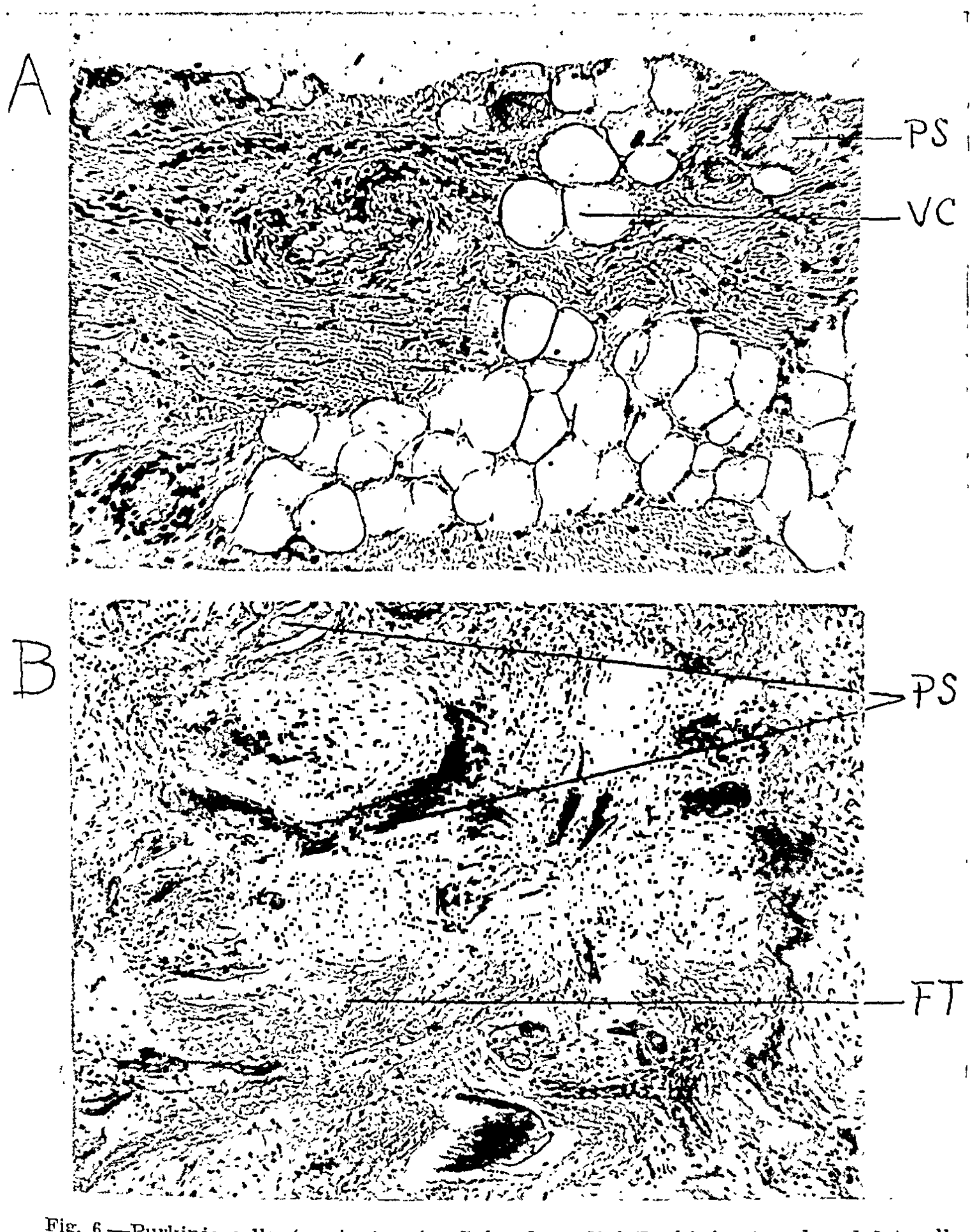


Fig. 6.—Purkinje cells (equine). *A:* Subendocardial Purkinje strand and fat cells (×110); *VC*, vacuolated cells; *PS*, Purkinje strand. *B:* Main His bundle (×90); *PS*, Purkinje strands; *FT*, fibrous tissue.

had read, in Mahaim's monograph, that gross dissection of the His bundle in man is impossible. Now, after having carefully studied the regions of the auriculoventricular node and the bundle of His in more than forty human hearts, we are quite ready to agree with Mahaim. A "special" conduction bundle cannot be found by gross dissection in the human heart. And we wish to add that the Purkinje system of the ungulate does not exist in man. However, the tissue which Mahaim and others describe as the bundle of His can be exposed by gross dissection. It is possible, without damaging the underlying muscular septum, to remove, bit by bit, the membranous septum, the connective tissue which forms the septal base for the tricuspid valve, and even the central fibrous body. When such a dissection is carried out, one finds that the upper ridge of the muscular septum is composed, in man, of a slender bundle of muscle fibers one millimeter or more in diameter. This forms the top of the ridge and runs into a canal in the central fibrous body. The lower part of this fasciculus continues underneath the base of the tricuspid valve, close to the septum membranaceum, runs subendocardially for a few millimeters, and then enters the muscular septum. Here the fibers spread out among the other myocardial elements. We have followed the slender strands into which this bundle divides for distances of five to ten millimeters in various directions in the myocardium and have found that they terminate like other subendocardial bundles. The "ridge" fasciculus is separated from the rest of the musculature by the same amount of interstitial tissue that is found elsewhere in the heart.

It is difficult to remove all of the fibrous tissue at the root of the aorta; but, when this is accomplished, and the endocardium is dissected away, the small fasciculi which Mahaim describes as the left branch can be seen distinctly and traced from their origin in the fibrous ring. Similar fasciculi are given off on the left side, not only in the region of the septum membranaceum, but also anterior and posterior to it. The strands where the bundle is supposed to bifurcate look exactly like those in front and behind it. Through the endocardium one sees frequently what appears to be the left branch of the His bundle. The "branch" seems to send one twig to the anterior, and one to the posterior, papillary muscle; but when the endocardium is removed, the illusion disappears, for the individual fibers which constitute this fasciculus are components of the septal muscle, which, after running a shorter or longer distance, terminate in the endocardium.

THE PURKINJE SYSTEM IN THE DOG

Gross Anatomy

Most of the experimental work on cardiac conduction in mammals has been carried out on the dog, on the assumption that a special conduction system exists in this animal, and that such a system consists of a sinoauricular node, an auriculoventricular node, and the bundle of His, with its ramifications. We have already reported our skepticism

concerning the existence of any specific conduction tissue in the sulcus terminalis of man, dog, sheep, cattle, horse, and hog (Glomset and Glomset[16]). Having failed to find, in man, a His-Tawara system of the type present in sheep and cattle, we searched for it in the dog. Fifteen canine hearts were dissected by the technique employed in our study of ungulate and human hearts. The muscle fasciculus which forms the upper part of the ventricular septum in the dog is strikingly similar to that in man. In this species, too, we believe that it is composed of ordinary muscle elements. It has been assumed that the visible fasciculus which runs from the base of the aortic valve toward the papillary muscles in the left ventricle is the left branch of the bundle. The dissection of the first canine heart convinced us that such is not the case, for this strand consists in the dog, as in man, of muscle fibers which have their origin at the base of the aortic valve. Subsequent careful histologic study of these fibers left us of the opinion that they differ in no essential feature from typical cardiac muscle.

MICROSCOPIC STRUCTURE OF THE HIS-TAWARA SYSTEM IN MAN AND DOG

A preliminary histologic survey of human and canine hearts convinced us that their so-called His-Tawara system differed radically from that found in sheep and cattle. Therefore, it became necessary to learn the histologic criteria used by other investigators. Prior to the year 1900, many investigators, including Purkinje, had failed to find Purkinje cells in human hearts, but, during the last three decades, the conviction that a special conduction system, containing Purkinje cells, exists in all higher animals has become fixed in the minds of cardiologists and physiologists. The various parts of the system are supposed to be found in the same localities in the dog and man as in the ungulates, and the form and structure are stated to be practically identical in canine and human hearts; but the histologic structure in man and dog is said to be different from that in sheep and cattle—so different, in fact, that only the trained eye of one who is continuously engaged in such studies can recognize and follow its ramifications (Winterberg[17]). Even such a person must study thousands of serial sections, and the loss of a single section may result in overlooking an essential lesion, or in losing the branch which is being followed (Mahaim).

In spite of the discouraging impression obtained from the literature, we decided to carry on, choosing for our differential criteria the descriptions of the microscopic structure of the His-Tawara system given by Tawara, Moenckeberg, Lewis, Mahaim, and Yater.

Table I epitomizes the conception held by these distinguished investigators of the minute anatomy of the conduction system in man and dog. A summary of the table follows:

The structure of the auriculoventricular node is not essentially different from that of the hoofed animals. It is smaller, the meshes are compressed, and a good-sized artery runs through it. (Mahaim's photo-

TABLE I

STRUCTURE OF HIS-TAWARA SYSTEM IN DOG AND MAN

		TAWARA, 1906	MOENCKEBERG, 1908	LEWIS, 1925	MAHAIM, 1931	YATER, 1938
Node of Tawara	Fiber mass	*Dog.* (Man—reticulum, less marked; meshes compressed.) Forms dense network; narrow, rounded meshes.	*Man.* Forms reticulum.	*Dog.* Man, similar to dog. Intricate interlacing; fibers cross and join at all angles.	*Man.* Macro: Ovoid, fan-like, imbedded in fat. Micro: Forms reticulum with wide meshes.	*Man.* Compared with Sinoauricular node. Reticulum, similar to S-A node; whorls; not so compact; less connective tissue.
	Individual	Slender, pale-staining; striations indistinct.	Compared with auricular fibers: Paler, vesiculated; striations: fewer, less distinct.	Slender, spindle-shaped.	Slender, pale-staining.	Thicker than in S-A node; striations more frequently visible.
	Nucleus	1, 2, rarely 3; round, oval, spindle-shaped.	More, larger, less chromatin.			
	Connections	Direct with auricular fibers; gradual change to bundle.	Direct with auricular fibers in front, above, and below.	Abrupt transition from auricular fibers.	Direct *connections to* auricle; gradual change from auricle to node.	*Fibers* merge with auricular myocardium; invade central fibrous body; become bundle *without* definite line of demarcation.
	Connective tissue	Separates fibers.	Much. More in old persons.	Dense network, holds fibers apart.		Less than in S-A node.
	Blood vessels and nerves		Large artery and veins at times; many capillaries; no nerve elements.	Arteries conspicuous; nerve fibrils and ganglion cells, scattered profusely.	Nerve and large artery accompanying node. Several arteries cross node.	Large artery usually runs through node.

Main Bundle	Macroscopic	Prism-shaped; broader at bifurcation.		Ensheathed in isolated canal.	Cannot be dissected out.	
	Microscopic Fibers	Fasciculi: "more parallel" than in node.	Slightly larger than myocardial fibers; vary in caliber, pipe-stem like.	Compared with nodal fibers: stouter "more parallel," in crease in size to arborization.	At first forms thin uniform network (like Tawara's node); later "more parallel"; not so easily distinguished. Poor staining.	Larger, "more parallel" than nodal fibers; resemble more ventricular fibers (not so much myoplasm). No true connective sheath.
	Fibrils and striations	Numerous, irregular; form network with small "Knoten."	Few fibrils, peripherally.		Cross striations, rare.	
	Nuclei	Many; round, oval, spindle-shaped.	Size: same as myocardial. Small amount of chromatin			
	Connective tissue	Surrounds fasciculi.	Surrounded by much connective tissue which sends septa into bundle.			No true connective tissue sheath.
	Artery Glycogen		Many capillaries and lymph spaces. No glycogen.	Glycogen present.	Artery accompanies bundle.	No main artery. Glycogen present.
Right Branch	Macroscopic	Narrow, cannot trace to termination.			Cannot be seen.	Whitish thread beneath endocardium.
	Microscopic	Similar to myocardial; fibrils parallel. Connective tissue separates fibers from ventricular muscle. Accompanied by branch from nerve trunk. Man similar to dog.	Fibrils parallel, compact, varying size, compared with ordinary muscle; difference in staining not marked, many nuclei; indistinct cross striations. Lower part enlarges, seen as yellow string; changes to Purkinje fibers which run subendocardially, contain glycogen.	Less distinct in human than in ungulate. Purkinje fibers present rich in glycogen.	Thin fibers, similar to those of trunk of node, closely packed; soon look like myocardial fibers.	Closely resemble myocardial muscle; same size or larger; paler, parallel, closer together; not always distinctly separated from cardiac muscle. Runs into myocardium; emerges to spread out as Purkinje fibers near base of anterior papillary muscle—beyond which not recognized.

TABLE I—CONT'D

		TAWARA, 1906	MOENCKEBERG, 1908	LEWIS, 1925	MAHAIM, 1931	YATER, 1938
Left Branch	Macroscopic and microscopic	Rather broad at origin; farther on still broader, separating finally into several parts. Strings running in trabeculae, usually to both papillary muscles.	Given off as fasciculi, separated by connective tissue. At first, fibers are similar to bundle: pipe-like, hollow, with definite cross striations and few bridges. Undergo alterations of structure, *finally* becoming more like Purkinje fibers.	Purkinje fibers present, rich in glycogen.	Spread out fan-like, subendocardially; never resemble myocardial fibers. *Soon become Purkinje fibers.*	
Purkinje Cells	General	Subendocardial. *Separated from* rest of heart muscle by *connective* tissue.	Slightly different from ordinary heart muscle. *Difference:* variation in size of cell, more sarcoplasm, lighter staining; fibrils fewer, variation in size, lighter staining, different arrangement. Rarely change to ordinary muscle.	"Transition to muscle abrupt; done by decreasing size and increasing striations," Tawara. Communicates with ventricular myocardium.		Recognized, rarely on right side of septum; never on lower left side. *Prominent* in periphery.
	Microscopic	Short, broad sarcoplasm "territories" with definite borders; constricted in places.	Empty space in sarcoplasm near nucleus; some hollow, some solid. Constricting cross striations at irregular intervals.	Swollen. Striations sparse.	Large, irregular, of unequal caliber; show knobs; vacuolated.	Large, pale. *Cross-striations readily* observed.
	Fibrils	Few, complexly arranged. (More in man.)		Poor in fibrils.	Very few.	Peripheral and prominent.
	Nucleus		Many forms: spindle-shaped. Lie in space free from fibrils.	Large, pale, frequently multiple.		
	Glycogen		Present always.	*Present.*		

micrograph shows two vessels, but no conspicuous reticulum.) The nodal fibers change gradually into the main trunk of the bundle. Here the fibers run "more parallel," are more voluminous, and contain more striations, i.e., they become "more like ventricular muscle." In the intramuscular portion of the right branch, the cells are so nearly like ordinary ventricular muscle fibers that if one serial section is missing the branch may be lost! The left branch is given off at various levels, beginning one to two millimeters anterior to the node, in the form of strands that do not make a definite, compact branch. The fibers "soon" change into Purkinje strands. All Purkinje cells lie subendocardially, and may or may not be surrounded by connective tissue sheaths. None of the five authors mentions a subendocardial Purkinje network. The Purkinje cells are usually larger than ordinary muscle fibers, have a clear space around the nucleus or nuclei, and have indistinct striations and irregularly arranged fibrils. They contain glycogen, and change imperceptibly into ordinary muscle fibers. Nerve elements are mentioned as occurring only in the node (Lewis).

Purkinje did not find the cells he described in man or dog. Todd[18] describes two kinds of Purkinje cells in man—the embryonic and the adult. The embryonic cell is large and polyhedral; it has irregular fibrils and few striations. The adult cell is more like the ordinary heart muscle fiber. Both types are found throughout the entire myocardium, from base to apex. Van der Stricht and Todd[19] state that all heart muscle fibers probably develop from Purkinje cells.

It is evident, then, that, in man and dog, the His bundle, its branches, and their ramifications differ strikingly from the same structures in sheep and cattle.

PERSONAL OBSERVATIONS

We examined the bundle region histologically in thirteen human and twelve canine hearts. The fresh tissues were fixed either in Bouin's solution or in a 10 per cent solution of formalin. Many of the dog hearts, and some of the human, were fixed while still warm. Sections were stained with iron-hematoxylin, hematoxylin-eosin, or Van Gieson. Complete serial sections were not made. Sections from the nodal regions were cut longitudinally and transversely from blocks that contained auricular wall, the central fibrous body, and the underlying ventricular septum.

Neither in the human nor in the canine heart did we see any muscular structure that looked like the node of Tawara, as seen in the hearts of sheep and cattle. Fig. 7*B* shows a section from the nodal region in man. It contains two branches of the septal artery and ordinary auricular muscle fibers.

We have studied many cross and longitudinal sections from the upper, middle, and lower parts of the septal ridge already described. Fig. 7*A* is a cross section of the ridge in man, and Fig. 8, *A* and *B*, is a

cross section of the ridge in the dog. As far as we can ascertain, the ridge is composed of ordinary ventricular muscle fibers both in man and dog. The microscopic structure of the subendocardial septal fibers in the left ventricle is seen in Fig. 9, *A* and *B*. We maintain that they, too, are ordinary muscle fibers that have been altered slightly in size and shape by their environment.

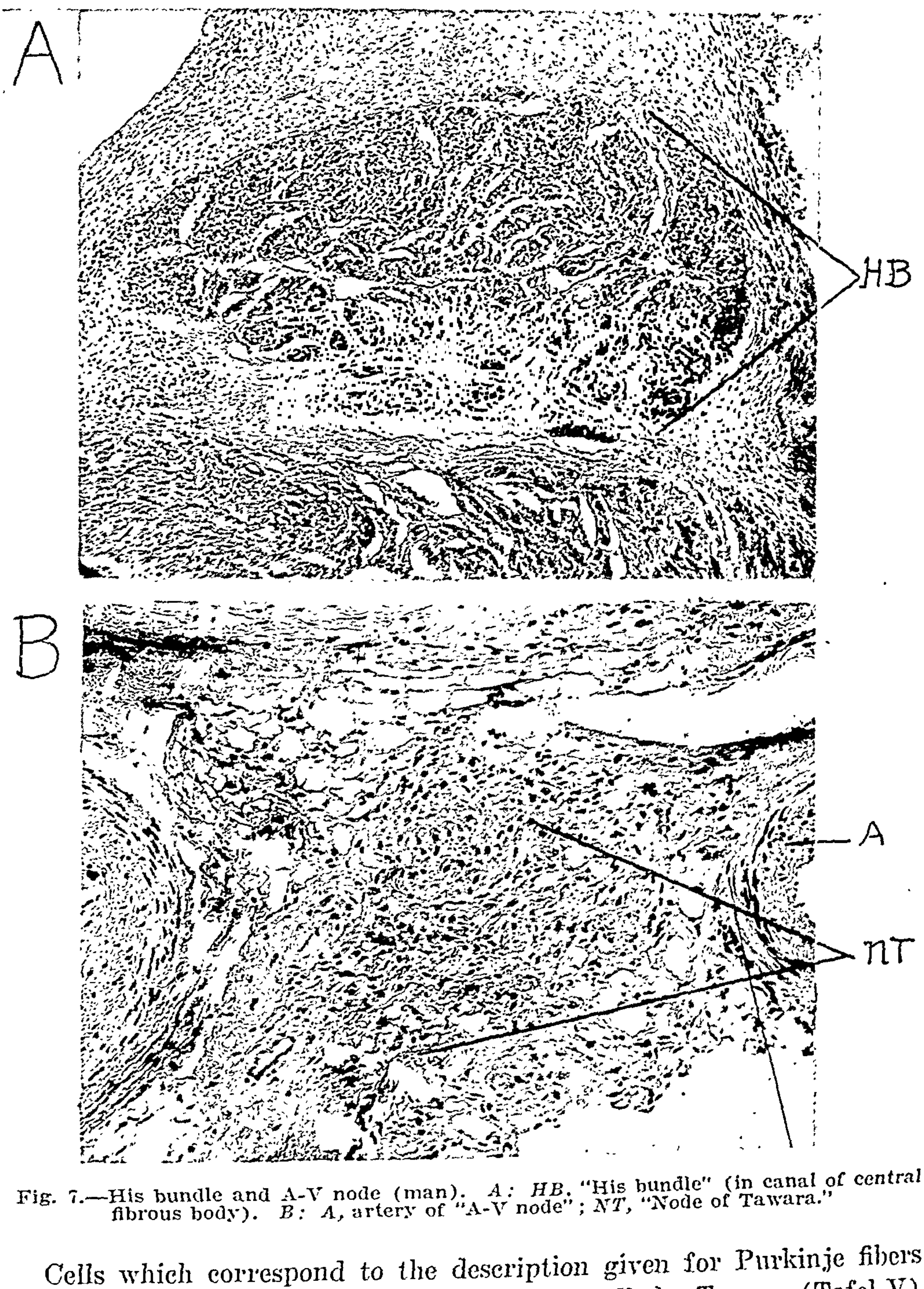
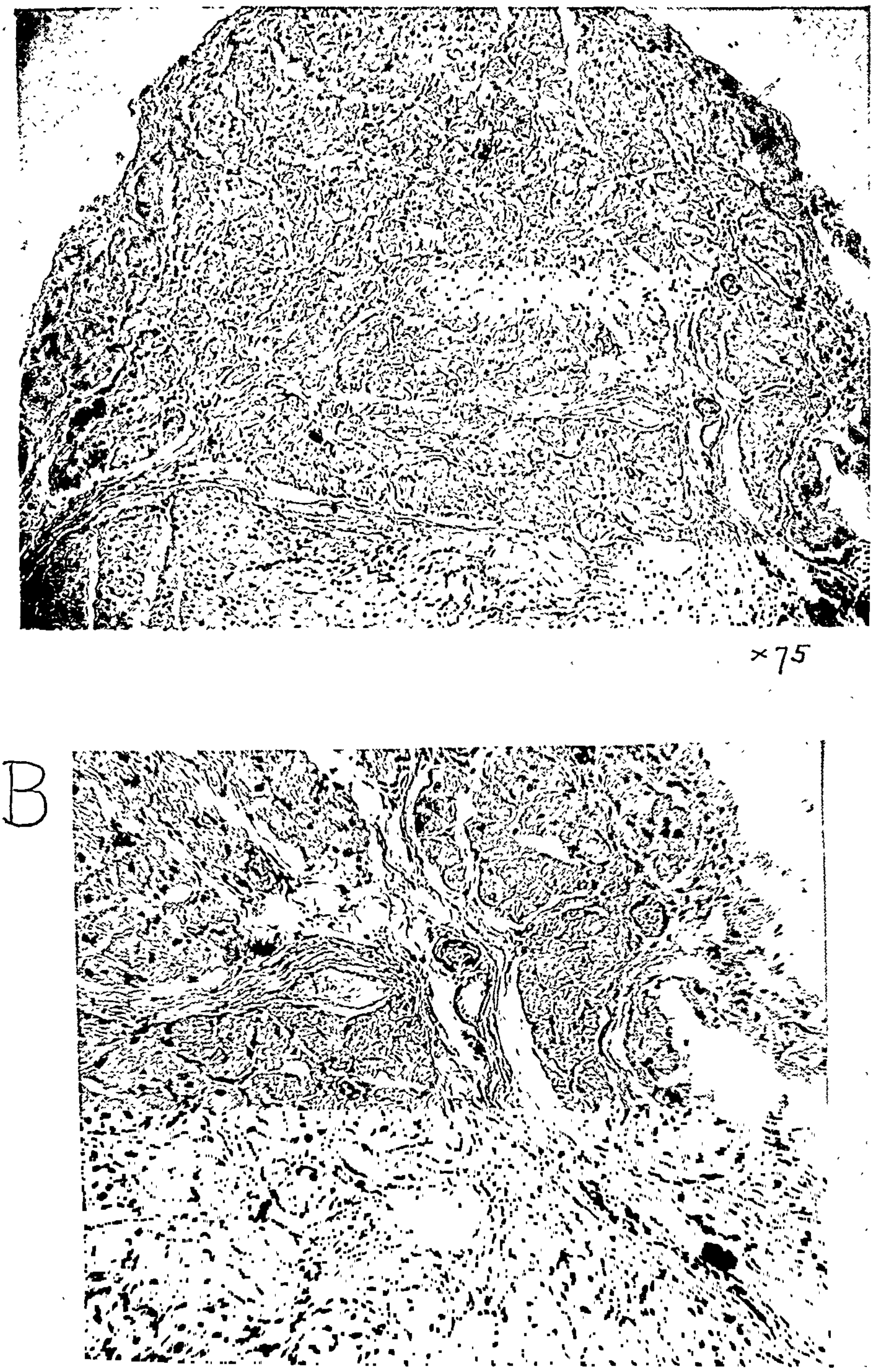


Fig. 7.—His bundle and A-V node (man). *A*: *HB*, "His bundle" (in canal of central fibrous body). *B*: *A*, artery of "A-V node"; *NT*, "Node of Tawara."

Cells which correspond to the description given for Purkinje fibers in man and dog and to the drawings of these cells by Tawara (Tafel V) are found under the endocardium in various parts of the ventricles. Such cells are often directly continuous with the ordinary myocardial

elements (Fig. 10*B*). Cells of this type are found occasionally under the pericardium and also in the deeper parts of the myocardium. They also occur in both right and left auricles. The "hollow" appearance of some of the "Purkinje cells," stressed by Moenckeberg, and the "vesicular" character, emphasized by other investigators, are probably artifacts, as suggested by Evans.[20] We have studied the region from

A



×75

B

Fig. 8.—Muscular ridge of septum (canine). *A:* ×40. *B:* Part of *A* (×100).

which Wachstein[21] obtained muscle strips for his study of contractility and conductivity of the Purkinje fibers. Fig. 10*B*, from this region, shows that such strips must have been composed of ordinary muscle fibers. Similarly, we have studied the pseudo-tendons from the ventricles of the dog, which Ishihara and Nomura[22] claim are composed entirely of Purkinje fibers. These, too, we believe to be ordinary cardiac muscle fibers (Fig. 10*A*). All elements held by others to be Purkinje cells, in man and dog, are different from the true Purkinje cells found in ungulates.

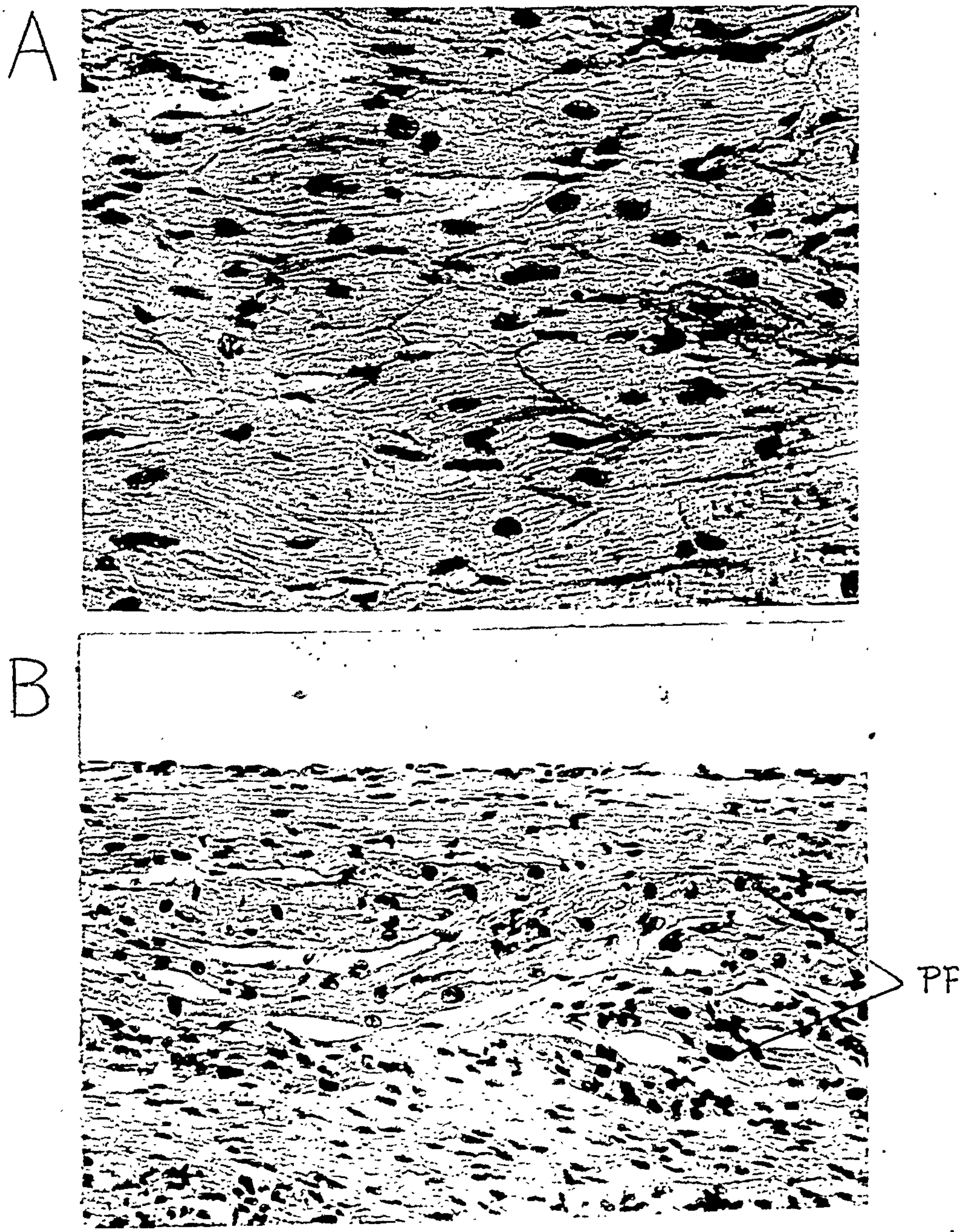


Fig. 9.—Cells from "bundle and left branch" (human). *A:* Muscle fibers of trunk (oblique). *B:* "Left branch"; *PF*, "Purkinje fibers."

Nerve tissue forms a conspicuous part of the conduction system in cattle, sheep, and swine. No mention is made of nerve elements in the structure described as the His-Tawara system in man and dog by the authors responsible for the information given in Table I, with the exception previously noted. Barton and Greenwood[23] and others found ganglion cells and nerve fibers in the nodal region in the dog heart. Our study disclosed both nerve cells and nerve fibers in this region. Nerves run in the atrial septum, and ganglion cells and bundles of nerves occur in front of, and behind, the central fibrous body in man and dog. These ganglion cells are a part of a wreath of nerve tissue which lies in the

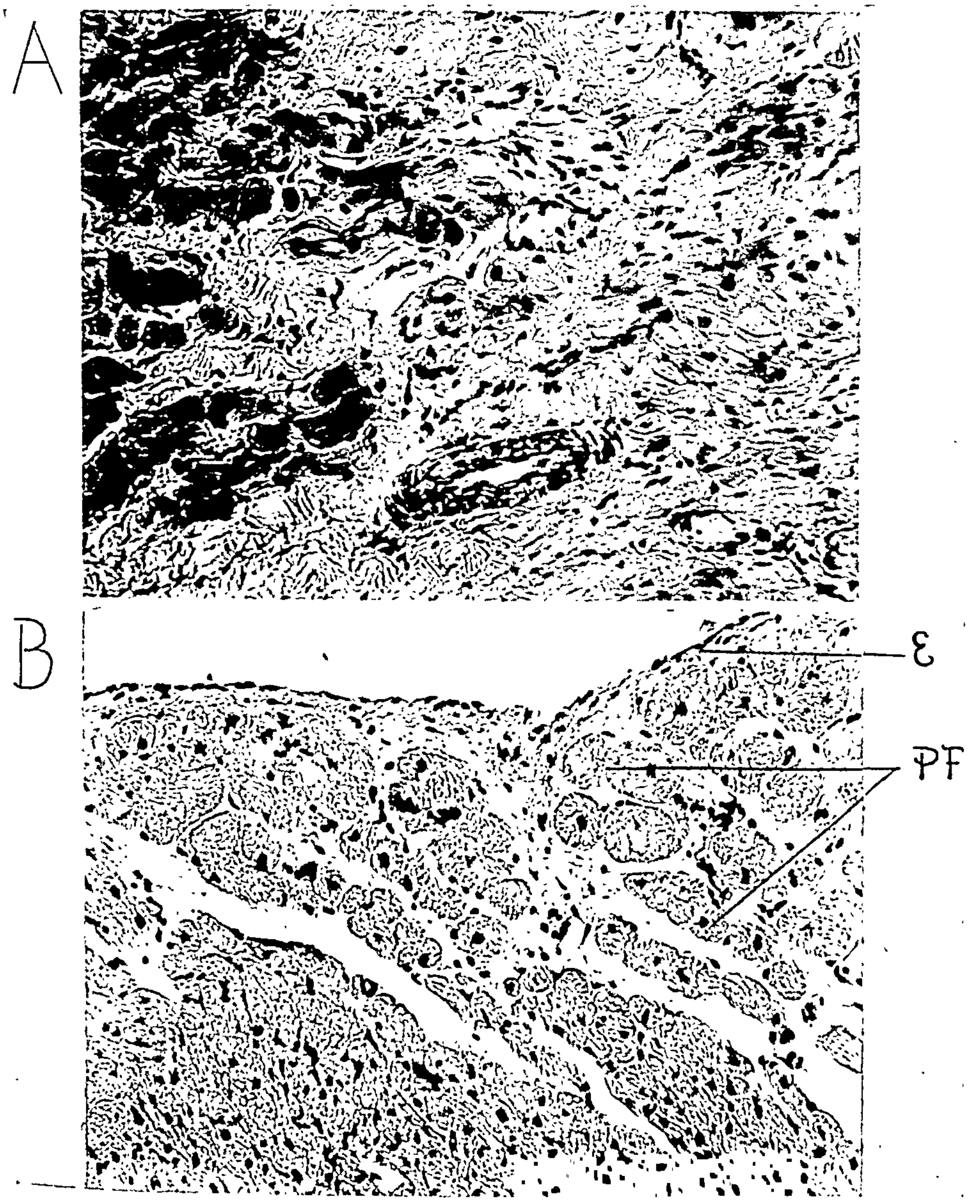


Fig. 10.—Purkinje fibers (canine). *A:* Section from pseudotendon. *B:* "Left branch," showing relation of "Purkinje fibers" to underlying myocardium; *E*, Endocardium; *PF*, "Purkinje fibers."

auriculoventricular groove. By special staining methods, Davies and Blair[24] demonstrated nerve twigs in what they took to be the His bundle and its branches in man. We found collections of nerve fibers throughout the myocardium of all of the cardiac chambers in man and dog; the nerve bundles, however, are smaller and fewer than in sheep and cattle.

GLYCOGEN

Marchand,[25] in 1886, observed glycogen granules in Purkinje cells. However, the idea that Purkinje fibers contain glycogen and that ordinary heart muscle does not appears to have originated in Aschoff's laboratory during the first decade of the present century (Aschoff and Nagayo[26]). Moenckeberg found glycogen in "Purkinje" cells, but none in the node of Tawara, the main bundle, or the right branch. Because of the prominence of the Aschoff group, their conception is widely known and generally accepted.

The present status of our knowledge concerning glycogen in Purkinje cells is excellently summarized in the article by Yater, Osterberg, and Hefke.[27] Glycogen can be detected in tissue by staining properly prepared sections with iodine or with Best's alkaline carmine, and the quantity of the substance present can be ascertained by chemical analysis. Histologically, glycogen has been demonstrated in the liver, skeletal muscle, Purkinje cells, tumors, and in ordinary cardiac muscle cells. Buadze and Wertheimer[28] found seven times as much glycogen in ordinary cardiac muscle as in the Purkinje cells of the horse. Yater, et al., found little difference between the glycogen content of ordinary heart muscle and the Purkinje fibers in the same animal, but great variation in individual hearts. Lewis[29] also noted that some artificially growing cardiac muscle cells contain glycogen granules, whereas others do not.

Our investigation of the glycogen content in tissue was limited to the study of sections stained with Best's carmine. Sections were examined from the anterior lower wall of the right ventricle of one sheep, from the same region and from the moderator band of a horse, and from the upper part of the septum of a two-hour-old baby. The tissues were submerged in absolute alcohol while they were still warm, and were imbedded in celloidin.

In the sheep, some Purkinje cells were "loaded" with red granules, and others contained none. In the horse, most of the Purkinje cells in the moderator band contained glycogen, and some of the large vacuolated polyhedral cells, lying subendocardially, were so crowded with granules that no cell structure could be seen. Others were free from the granules. In the septum from the baby, no large granules were found in any cell, but a faint pink stain was taken by most of the muscle elements. Both in the horse and in the sheep, small red granules were seen here and there in the endothelium of the endocardium, and also in the interstitial tissue.

From the information obtained in the literature, and from our own experience, we gain the impression that the presence of intracellular glycogen granules, as shown by staining with iodine or carmine, does not constitute a distinguishing feature of Purkinje cells.

COMMENTS

If one accepts the assertion that the structures described by the authors cited in the table constitute the special cardiac conduction system in man and dog, one is forced to concede that similar physiologic properties are possessed by tissues which are strikingly dissimilar morphologically, for the difference between the two nearly identical "His-Tawara systems" in dog and man, and the Purkinje system in ungulates, are many and significant. These are as follows:

1. A definite, easily recognizable structure, the node of Tawara, exists in cattle, sheep, and hogs. There is no such node in man or dog.

2. In sheep and cattle, the cells at the edge of this node change abruptly to strikingly different, binucleated Purkinje cells. These, without altering shape or structure, run in strands through the main bundle and its branches, form a subendocardial network, and penetrate the entire myocardium of both ventricles and the septum. In man and dog, however, it is admitted that Purkinje cells do not exist in the main bundle nor in the upper part of the right branch. The cells which are described as Purkinje elements in the left branch and lower right branch differ strikingly from those found in sheep and cattle. They do not form a network, are found only subendocardially, and have never been recognized within the myocardium.

3. In the upper part of the main bundle in sheep, cattle, and hogs, where nodal cells change into Purkinje elements, large numbers of nerve fibers enter the bundle. These form a conspicuous part of the main trunk and its branches; they also accompany the smaller strands. Ganglion cells are frequently found at the periphery of the main bundle and its right and left branch. Such nerve elements are found neither in the "bundle" nor in its subdivisions, in man or dog.

4. In sheep and cattle, the trunk, its branches, and their minute ramifications are surrounded by a distinct sheath of connective tissue. This permits visualization of the whole system after injection with suitable material. No such sheath is found in man or dog, and many attempts at injecting the system in these species have failed.

SUMMARY

Sheep, Cattle, and Swine

1. A distinct, ventricular Purkinje system has been found in sheep, cattle, and swine. This begins in a node which lies at the top of the ventricular muscular septum, near the posterior part of the central fibrous body in the right side of the heart. The fibers of this node do not have a direct connection with the auricular muscle fibers, but run in

strands which spread out over the posterior upper part of the ventricular septum, and even enter the right ventricle.

2. Only the anterior part of the node changes abruptly into the characteristic Purkinje cells, which run in strands through the bundle and its main branches, and form a subendocardial and intramuscular network in the ventricles.

3. Numerous nerve fibers and ganglion cells form a conspicuous and significant part of the His bundle and its ramifications.

4. The bundle, its branches, and the Purkinje network are surrounded by a sheath of connective tissue. Nowhere in the system have we seen the Purkinje cells change into ordinary ventricular muscle.

Man, Dog, and Horse

5. In the horse a vestigial remnant of the Purkinje system is present.

6. In the dog and in man the local modifications of structure in the homologous positions do not appear to us to possess the characteristic features exhibited by the conduction systems of sheep and cattle.

7. Cells, in human and canine hearts, which are considered by others to be Purkinje elements, have been found in the atrial and ventricular musculature of the hearts of all of the species that we have studied.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING METRAZOL-INDUCED CONVULSIONS

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DURING the treatment of psychotic patients with metrazol,* it has been reported by others,[1, 2, 3] and noted frequently by us, that immediately following the convulsion there is a pronounced, but temporary, cardiac arrhythmia. These observations together with the tremendous violence of the treatments, aroused our interest and led us to study the cardiac mechanism following metrazol-induced convulsions.

Electrocardiograms were taken on thirty-seven patients before and after forty-three convulsant doses and nine subconvulsant doses of metrazol. The three standard leads were taken just preceding the injection of the drug, and Lead II was again recorded immediately upon cessation of the convulsion, and at three, five, and ten minutes after the injection. Before the adoption of this procedure, it had been ascertained by taking tracings over a two-hour period that most of the significant changes occurred within the first ten minutes after injection of the drug. In some cases the patients became so violent that it was necessary to disconnect the galvanometer before the observations were complete. Whenever possible, the blood pressure was recorded simultaneously.

Table I

Age Distribution in Decades

Age in years	10-19	20-29	30-39	40-49	50-59	60-69
Number of cases	1	4	15	12	4	1

The patients' ages ranged from 19 to 65 years; the distribution by decades is shown in Table I. Sixteen of the patients were from private psychiatric practice, and the remaining twenty-one were inmates of a state institution. In all but five of the cases, which will be considered in detail later, the cardiovascular system was normal. Metrazol was used in a 10 per cent solution and was injected as rapidly as possible through an 18-gauge needle into one of the large veins of the antecubital fossa.

The major portion of this report deals with the changes which were observed when convulsant doses of the drug were administered. The effect of subconvulsant doses is discussed separately.

CHANGES IN BLOOD PRESSURE

Blood pressure measurements were made coincidentally with the electrocardiograms after thirty-one of the forty-three convulsions, and in all but two instances there was a sharp rise (Table II). The systolic pressure always rose more than the diastolic; the mean increases were 45 mm. Hg and 19 mm. Hg, respectively.

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*Metrazol (Cardiazol) is the proprietary name of pentamethylenetetrazol. It resembles camphor in many of its actions and is a strong convulsant and medullary stimulant.

TABLE II

CHANGES IN BLOOD PRESSURE

CASE NO.	CONTROL	IMMEDIATELY AFTER CONVULSION	3 MIN. AFTER INJECTION	5 MIN. AFTER INJECTION	10 MIN. AFTER INJECTION
2	120/80			170/100	132/82
3	135/80	180/110	200/130	160/100	135/90
5	170/110	210/100		190/90	150/70
6	160/90		190/90	160/70	
7	160/100	180/130	150/90	140/80	135/70
8	155/90	200/100	185/80		150/70
9	145/80	160/90	150/70	110/50	
11	155/90	210/100		170/90	140/85
13	140/90	180/100	150/80	150/80	150/80
14	145/80	170/100	165/100		120/70
15	140/90	135/70	135/60	120/60	
16	130/80		160/60	125/55	125/55
17	130/70	150/80		140/???	
20	140/90	195/90		170/100	140/80
20	150/90		200/110	160/70	135/70
23	150/90	185/100		185/90	160/90
24	150/90	190/100			130/85
25	120/80		130/80		110/70
26	130/85	185/120			
27	155/100	210/100		140/75	130/85
27	110/70	180/100	150/80		120/80
28	130/80	150/90	120/70		
29	150/94	150/90			
30	120/80	175/100	175/100	130/70	110/70
31	118/80	140/85	140/85	118/70	118/70
32	170/90	220/100	220/120		
33	120/80	195/100	168/100	140/75	140/75
33	110/70	170/90		140/90	110/70
34	210/110	300/120	250/120	220/90	220/90
35	100/70		140/80		
36	115/50	130/70	140/80	125/80	
37	160/100	150/110		200/120	140/90

Similar changes in blood pressure following metrazol convulsions in man have been reported by Hadorn,[2] and Forschbach,[3] and in animals by Müller.[4] These observations do not agree with those of Messinger and Moros;[1] we are unable to explain this fact, for their measurements were apparently made at approximately the same time after the convulsions.

CHANGES IN HEART RATE

Although variations in the cardiac rate were observed in all instances, there was no consistency in the direction or magnitude of these changes. If a change of twenty-five cycles per minute is arbitrarily assumed to be significant, cardiac slowing, cardiac acceleration, and no significant change in heart rate occurred with equal frequency. In a few instances the change in heart rate was conspicuous; in one, the rate fell from 136 to 38 per minute (Fig. 1*B*). The bradycardia was the result of temporary, complete A-V dissociation. In other instances the cardiac slowing was associated with inversion of the P deflections, indicating that the pacemaker had shifted to the A-V node. Sinus tachycardia occurred frequently; in one instance the heart rate rose to 160, and, in two others, to 176 and 177, respectively.

CHANGES IN RHYTHM

Gross cardiac arrhythmia was conspicuous immediately after all but eight of the forty-three convulsions. The disturbances in cardiac mechanism were of three types: those characterized by changes in the heart rate and location of the auricular pacemaker (Figs. 1 *A* and 2); those resulting from variations in A-V conduction (Fig. 1); and those caused by extrasystoles of various types (Fig. 3).

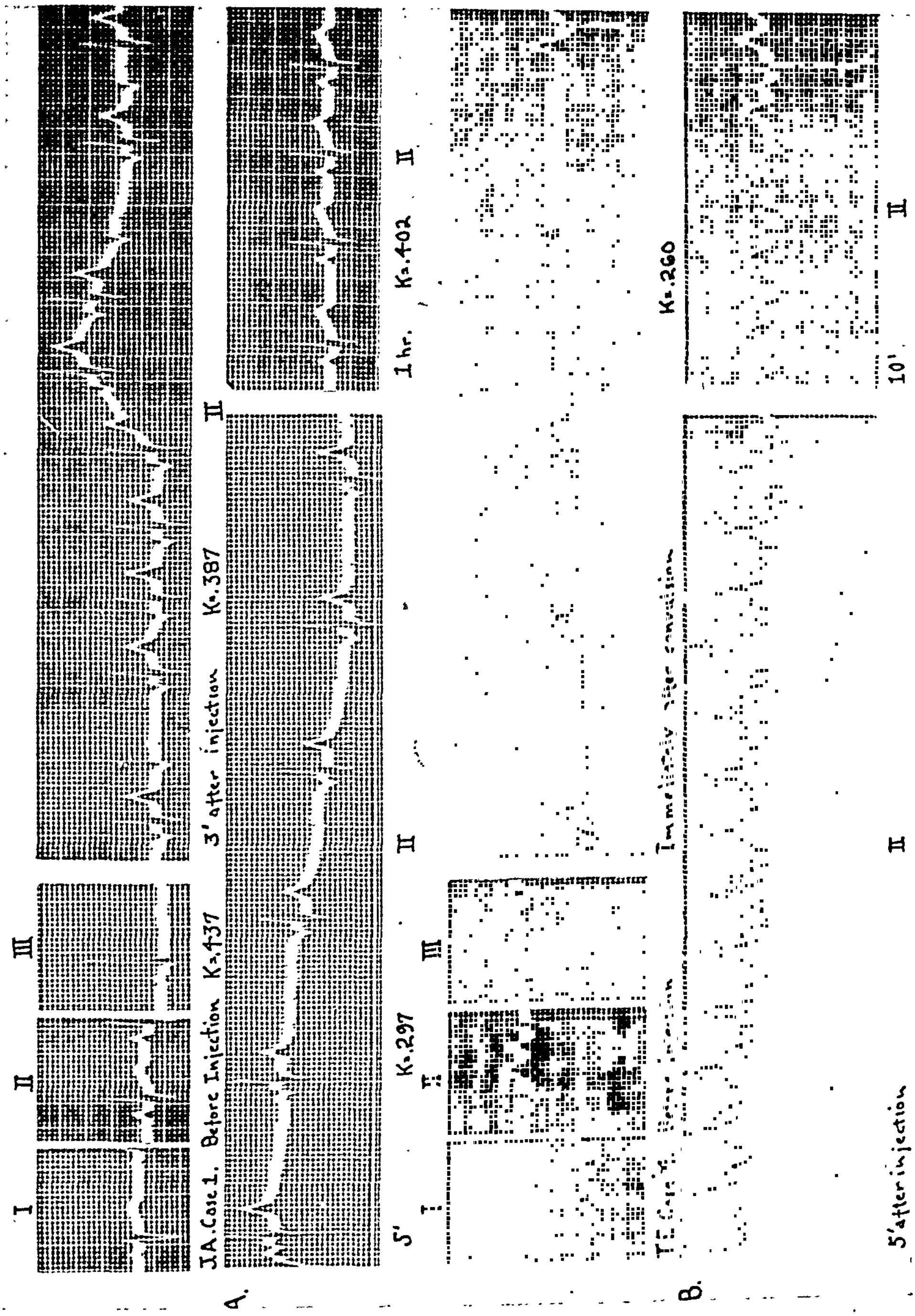

Fig. 1.—*A*, Case 1. A-V rhythm, with partial heart block, immediately following the convulsion. K is reduced, and there is a marked change in the contour of the T waves. *B*, Case 4. Complete A-V dissociation, with interference, immediately following convulsion. K is reduced, and there is a change in the T waves similar to that in *A*.

In some records only one of these disturbances was present, but more often two, or all three, of them occurred together. Table III indicates the various frequencies of each. Our records (Figs. 1, 2, and 3) are, for the most part, similar to those published by others.[2, 3] Although auricular fibrillation has been referred to frequently[2, 5, 6, 7] as a complication of the metrazol-induced convulsion, it was not observed in a

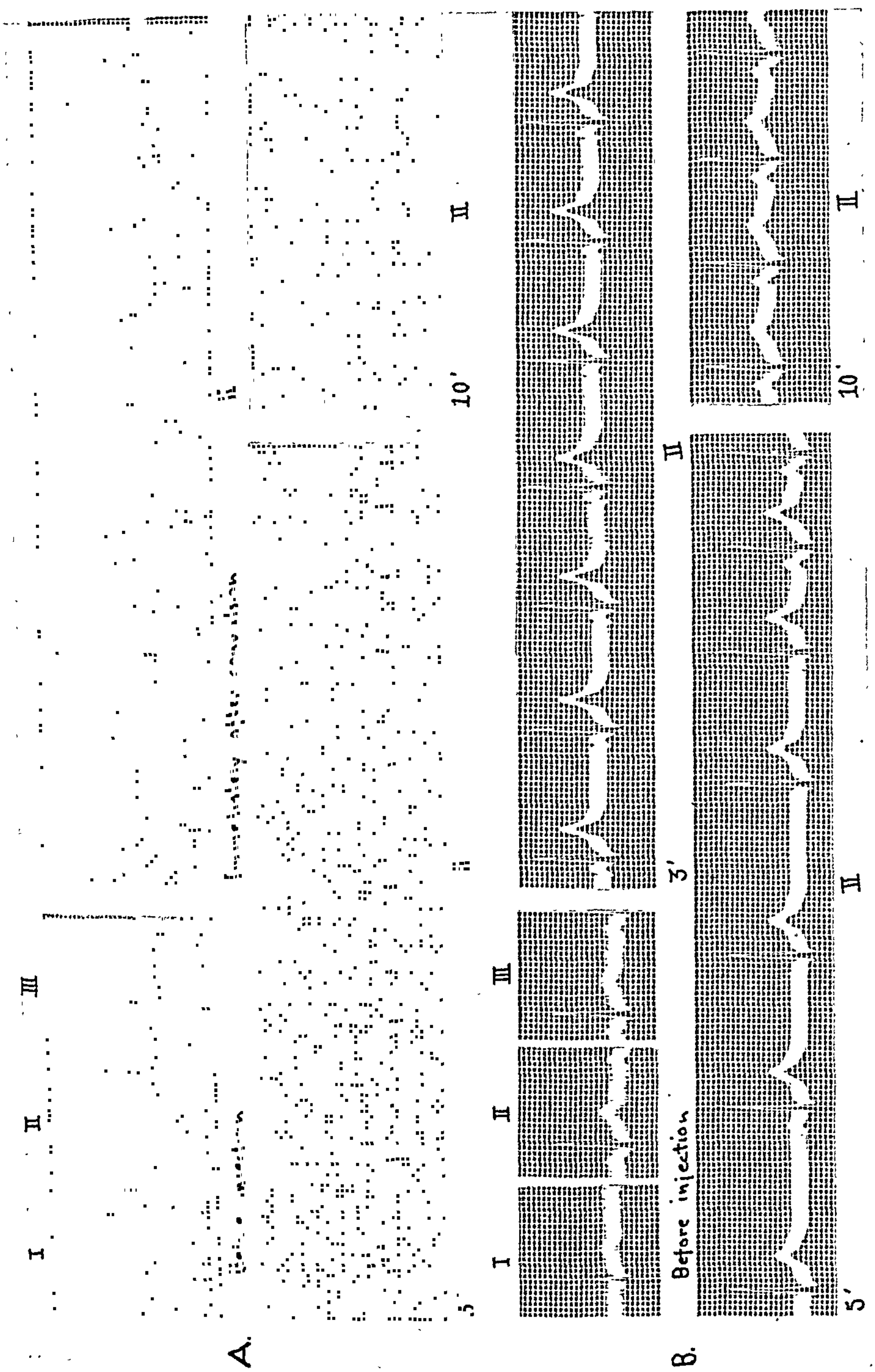

Fig. 2.—*A*. Case 5. Shifting pacemaker and ventricular extrasystoles immediately following convulsion. *B*. Case 11. A-V rhythm following convulsion.

TABLE III

TYPE AND FREQUENCY OF ARRHYTHMIAS

TYPE	NO.
Sinus arrhythmia (marked)	4
Shifting pacemaker	15
Atrioventricular rhythm	10
Prolonged P-R interval	3
Partial heart block	2
Complete A-V dissociation, with interference	2
Auricular extrasystoles (including one case of bigeminy)	19
Auricular extrasystoles (blocked)	1
Atrioventricular extrasystoles	4
Ventricular extrasystoles (including one case of bigeminy)	4
Number of convulsions following which the above observations were made	35
Number of convulsions following which no significant arrhythmia was observed	8
Total number of convulsions studied	43

single instance in this series. It should be pointed out that the great frequency of pronounced arrhythmias of other varieties makes the diagnosis of auricular fibrillation difficult, under the circumstances in question, unless an electrocardiogram is taken. Examination of our records clearly indicates the difficulty, if not the actual impossibility, of distinguishing clinically between these arrhythmias and auricular fibrillation. An electrocardiogram was taken in only one of the three cases of fibrillation reported by Dick and McAdam,[5] and this electrocardiogram was described as showing "partial flutter." Lubner[7] also reported a case of auricular fibrillation but made no mention of electrocardiographic confirmation.

The mechanisms responsible for the striking alterations in the rhythm of the heart which we observed are at the present time not definitely known. It seems probable that the changes in the location of the pacemaker were the result either of powerful vagal stimulation induced by the sudden increase in blood pressure, which occurred in most of the cases at approximately the same time, or of direct drug action. The disturbances in A-V conduction may be attributed to the same cause, or to anoxemia secondary to the convulsion. From our records, it was not possible to decide which of these factors was the more important, for both increased vagal tone and anoxemia depress the conductivity of the A-V node.[8] It should be noted that Erickson[9] and Hadron[2] did not observe cardiac arrhythmia in association with the spontaneous convulsions of epilepsy. The former states that the change in blood pressure during epileptic convulsions is extremely variable. To investigate further the cause of the cardiac arrhythmia in metrazol shock, it would have been desirable to repeat some of our observations after thorough atropinization, but under the circumstances of this study it was not possible to do this.

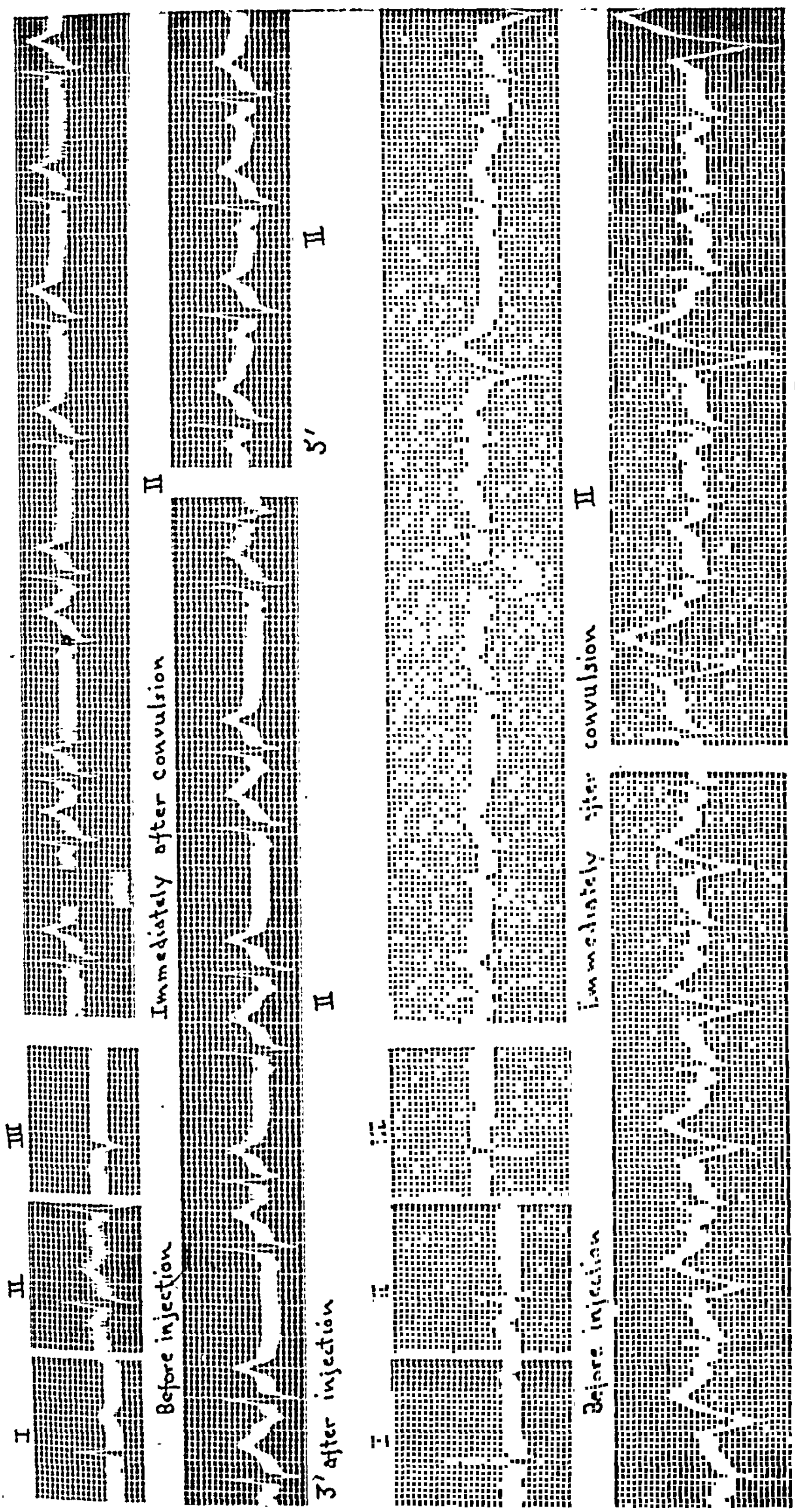

Fig. 3.—*A*. Case 29. Bigeminal rhythm produced by auricular extrasystoles. *B*. Case 37. Bigeminal and quadrigeminal rhythm produced by ventricular extrasystoles. T waves in Lead II became upright immediately following the convulsion.

CHANGES IN THE T WAVE

An increase in the amplitude of the T wave has been noted by others,[1] and occurred in the single lead which we recorded (Lead II) during thirty-three of the forty-three convulsions. This change was almost always most pronounced in the record which was taken immediately following the convulsion; in every instance the T wave had returned to its original amplitude by the end of the ten-minute period of observation. Although the increase in the height of T was usually no more than 1-2 mm., it was occasionally much greater. In Case 4 (Fig. 1 *B*), the height of the T wave increased from 5 mm. in the control record to 10 mm. in the record which was taken five minutes after the injection of metrazol. In two instances (Fig. 3 *B* and Case 34, Fig. 4), T waves which had been negative in Lead II in the control curve became positive following the convulsion.

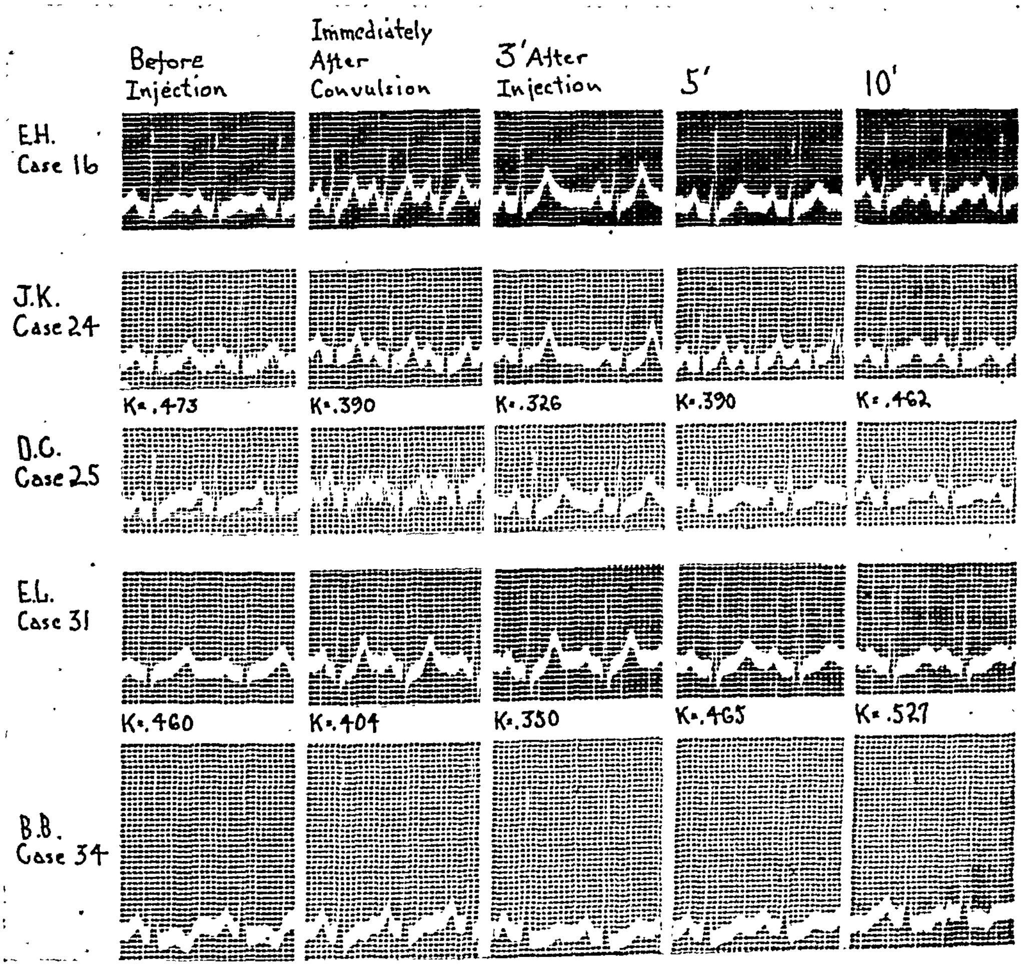

Fig. 4.—Cases in which the principal change following the convulsion was in the magnitude and contour of the T wave. Lead II throughout.

A change in contour accompanied this increase in height of the T wave. This change is illustrated in Fig. 4. The T waves rise more abruptly than in the control curve, are more sharply pointed, and appear narrow, as if the ascending and descending limbs had been pressed closer to-

gether. Barker and his collaborators[10] reported similar changes in the T waves when the blood pH was lowered by the ingestion of ammonium chloride, strenuous exercise, or rebreathing. Low and his co-workers,[11] who studied some of the physiologic changes which accompany metrazol convulsions, found a reduction of the blood pH from a mean fasting level of 7.34 to a mean level of 7.14 ten minutes after the convulsion. Although these authors caution against drawing far-reaching conclusions from such a small number of observations (ten patients, ten controls), it is possible that the changes in the T waves which we observed were the result of a temporary acidosis.

CHANGES IN THE DURATION OF ELECTRICAL SYSTOLE

In order to take into account the variation of electrical systole which occurs with changes in the heart rate, we have applied the formula of Bazett[12] (systole $= K\sqrt{\text{cycle}}$), using K as an expression of the duration of systole. Bazett found that, in normal men, K varied between 0.342 and 0.392, with an average value of 0.368. In normal women, K varied between 0.36 and 0.44, with an average value of 0.399.

In our series it was found that K was reduced (0.030, or more) immediately after the convulsion in thirty-two instances, was increased in eight, and remained unchanged in three. In fourteen cases, K was found to be well above the upper limits of normal ten minutes after the injection of the drug.

In those cases in which K was appreciably reduced, there was a concomitant increase in the amplitude of the T wave; this suggests that these two changes were interdependent. Examples of this association are shown in Fig. 1. The striking variations in K were caused mainly by changes in heart rate without corresponding alterations in the Q-T interval, but in part by changes in the Q-T interval itself.

OBSERVATIONS FOLLOWING SUBCONVULSANT DOSES

Occasionally, during the course of treatment, a dose of metrazol which was ordinarily large enough to produce a convulsion would fail to do so. This was particularly true of the initial treatment. At the outset we had hoped that a study of the changes produced in the electrocardiogram by subconvulsant doses would differentiate the direct effects of the drug alone from the indirect effects of the convulsion. It was soon learned, however, that patients were so disturbed by subconvulsant doses that technically satisfactory records were difficult to obtain. Nine satisfactory records were obtained.

Except for minor deviations, the electrocardiograms which were taken at intervals after such injections in seven patients were not essentially different from those of the controls.

In two cases, however, changes in the cardiac rhythm were conspicuous. Fig. 5 *A* and *B* shows the electrocardiograms in Case 29; one set (5 *A*) was recorded following a subconvulsant dose of metrazol, and

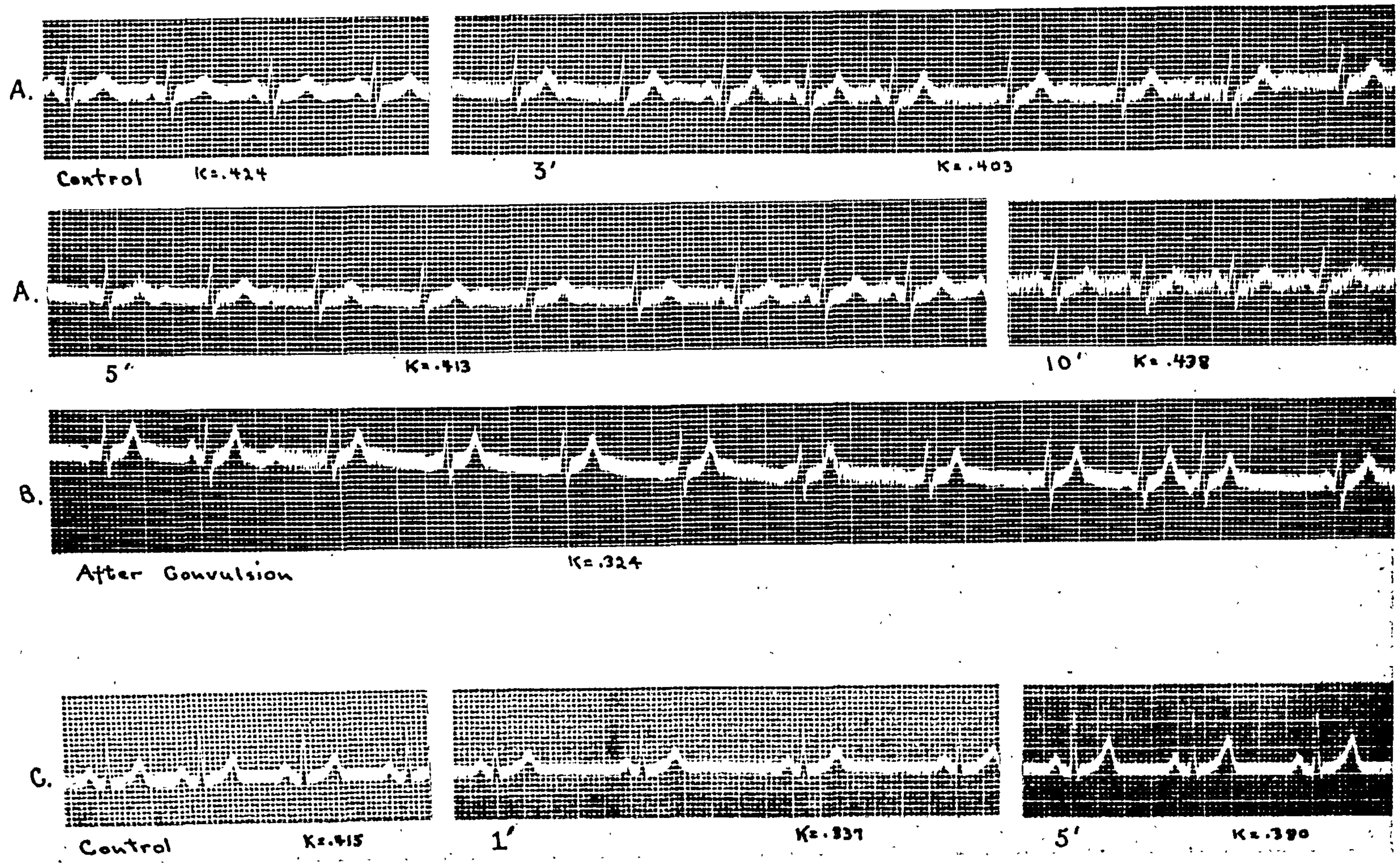

Fig. 5.—Lead II. *A*. Case 29. A-V rhythm 3 and 5 minutes after a subconvulsant dose of metrazol. *B*. Immediately following a convulsion produced by a second injection. In this record there is a change in the contour of the T waves and a reduction in K. *C*. Case 35. Sinus bradycardia following a subconvulsant dose. In this case there are a reduction in K in the three-minute record and an increase in the magnitude of the T waves in the five-minute record.

the other (5 *B*), after a typical convulsion had been produced by a second injection, twenty minutes after the first. In both records atrioventricular and sinus rhythm alternated, although, after the convulsion, the A-V rhythm was more persistent and was accompanied by numerous auricular extrasystoles. The second set of records, but not the first, showed the typical changes in the contour and amplitude of the T wave and in the value of the systolic index "K" which have already been referred to. The value of K was 0.403 during the period of A-V rhythm which was induced by the subconvulsant dose of metrazol, but only 0.324 after the A-V rhythm which followed the convulsion.

The electrocardiograms shown in Fig. 5 *C* were obtained in Case 35, in which there was sinus bradycardia, with a rate of 53 per minute, immediately after a subconvulsant dose. In contrast to the other case illustrated in this figure, the subconvulsant dose of metrazol was followed by an increase in the magnitude of the T waves and a reduction in the value of K from 0.415 to 0.337.

The changes in rhythm which follow the injection of a dose of metrazol which is insufficient to provoke a convulsion may be the result of central vagal stimulation. The modification of the T waves and of K which is sometimes seen under these circumstances cannot be ascribed to the same cause.

CASES IN WHICH THE CARDIOVASCULAR SYSTEM WAS ABNORMAL

Included in this series were five patients whose cardiovascular systems were either questionably normal or definitely abnormal. There was considerable hesitation about recommending metrazol treatment for these patients, but when the hopelessness of their mental state was considered, the risk seemed worth taking. The essential clinical features in these cases are outlined in Table IV. Except for one case of mitral stenosis, the cardiac abnormalities in this group were probably the result of hypertension and arteriosclerosis.

The control electrocardiograms of these five patients are shown in Fig. 6. Contrary to our expectations, the records taken following the convulsion in this group did not differ from those obtained after the convulsion in subjects with normal hearts. The treatments were tolerated equally well and were completed uneventfully in each instance.

In retrospect, however, it seems probable that the successful completion of treatments in these cases was partly the result of good fortune, particularly in Case 34, and to a somewhat less degree in Case 23. In Case 34, in addition to the patient's advanced age of 65 years, there were a consistent elevation of the systolic blood pressure (over 200 mm. Hg) and a grossly abnormal electrocardiogram. Furthermore, the systolic blood pressure rose to 300 mm. Hg immediately after the convulsion on at least two occasions. It could be lowered to its former level by means of amyl nitrite. Judging from this observation, a sustained systolic blood pressure of more than 200 mm. Hg substantially increases the risk of this type of treatment.

TABLE IV

CASES IN WHICH THE CARDIOVASCULAR SYSTEM WAS ABNORMAL

CASE	AGE	PSYCHIATRIC DIAGNOSIS	CARDIAC DIAGNOSIS	HEART SIZE (FLUOROSCOPY AND TELEOROENTGENOGRAM)	BLOOD PRESSURE	ELECTROCARDIOGRAM (SHOWN IN FIG. 6)	NO. OF TREATMENTS
T. E. Case 4 Female	53	Simple depression	Questionably abnormal electrocardiogram	No enlargement	150/90	Left axis deviation not definitely outside normal limits. White's index +24	5
J. C. Case 6 Male	48	Manic depressive, depressed	Hypertensive heart disease; latent syphilis	Enlargement of left ventricle	160/90	Marked left axis deviation. Index +37	12
N. L. Case 23 Female	30	Dementia praecox	Rheumatic heart disease; mitral stenosis and insufficiency	Enlargement of all chambers	150/90	Right axis deviation not definitely outside normal limits. Index −13	31
B. B. Case 34 Female	65	Simple depression	Hypertensive heart disease	Enlargement of left ventricle	215/105	Abnormally large QRS complexes and inverted T waves in Leads I and II	6
T. K. Case 37 Male	50	Simple depression	Hypertensive heart disease	No enlargement	150/110	Rather flat T waves in Lead I, with inversion in Lead II. Left axis deviation. Index +21	7

The only patient in this series with chronic valvular disease (Case 23) tolerated a prolonged course of treatments, thirty-one in all, surprisingly well. It should be emphasized, however, that at no time were there any signs of cardiac failure. Any evidence of cardiac failure would in itself have contraindicated metrazol treatment.

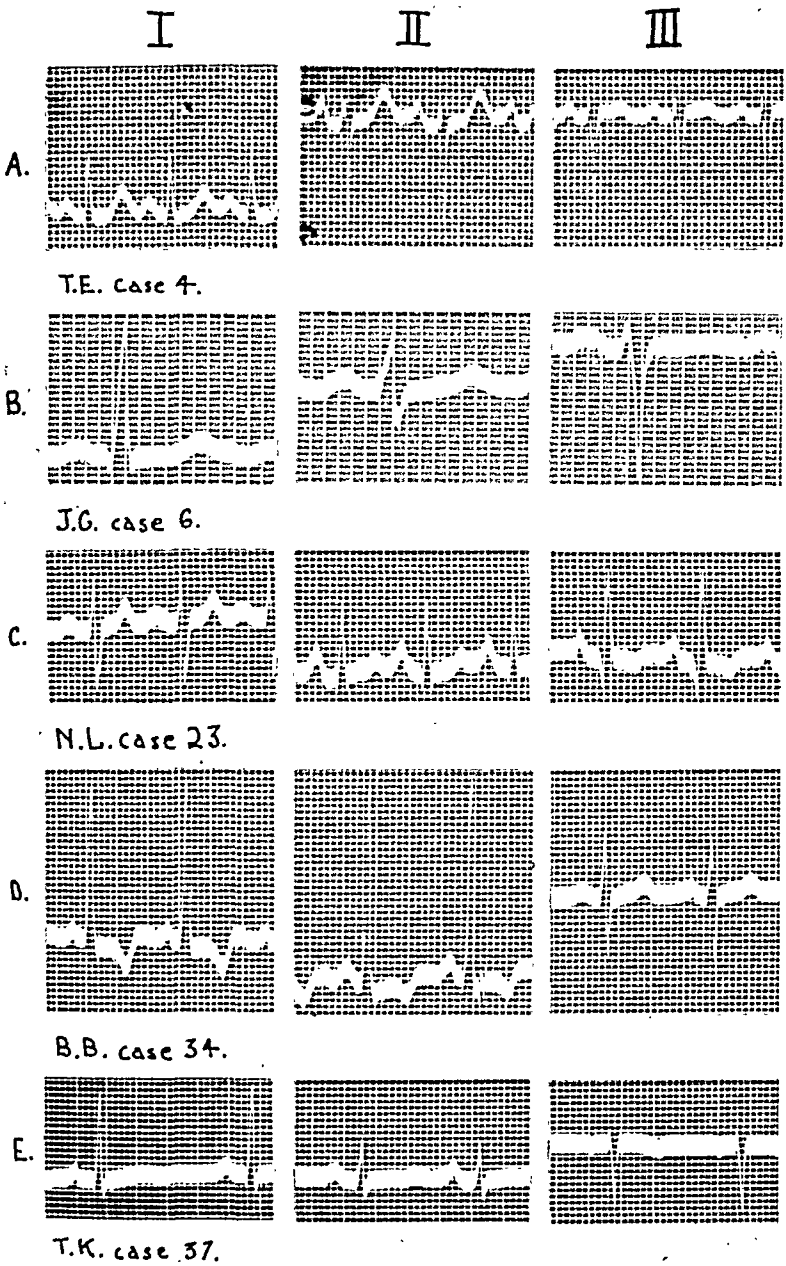

Fig. 6.—Control electrocardiograms of the patients listed in Table IV.

SUMMARY AND CONCLUSIONS

Observations were made following forty-three metrazol-induced convulsions and after nine injections of the drug in amounts which were insufficient to provoke a convulsion. Invariably, there were a rise in

both the systolic and diastolic blood pressure and a change in the heart rate; the latter was inconstant in direction and magnitude.

The most striking disturbances were the frequent and varied arrhythmias which followed most of the convulsant doses and several of those which failed to induce a convulsion. These changes in the cardiac mechanism were probably the result of increased vagal tone and other factors, such as asphyxia.

After the convulsions the T waves of the electrocardiograms became tall and pointed, and the value of the Bazett systolic index (K) was greatly reduced.

No permanent alterations of the cardiac mechanism occurred.

We wish to thank Dr. Harold Feil and Dr. Frank N. Wilson for their help in the preparation of this manuscript.

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THE PERIPHERAL BLOOD FLOW IN HYPERTHYROIDISM

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INTRODUCTION

SINCE 1825, when the posthumous papers of Parry, including a description of hyperthyroidism, were published, clinicians have been impressed by the changes which this disease occasions in the cardiovascular system. Studies have been made of the basal metabolic rate,[1] cardiac output,[2, 3, 4] blood volume and venous pressure,[5, 6] velocity of blood flow,[6, 7] pulse rate and pulse pressure,[8, 9] and vital capacity[10, 11] before and after treatment. The flushed appearance of these patients points to a change in the peripheral circulation. No objective measurements of peripheral circulation, however, have been made.

We have measured, therefore, the peripheral blood flow of eighteen patients who had signs and symptoms of hyperthyroidism (1) when they first came under observation, (2) while they were receiving iodine, and (3) after thyroidectomy. Since the methods we employed were relatively new, a review of pertinent observations is in order.

RÉSUMÉ OF LITERATURE RELATIVE TO RADIATION, CONDUCTION, CONVECTION, AND EVAPORATION

Rubner[12] was the first observer to grasp the significance of heat loss. In 1896, he published a table estimating losses from radiation and convection. The thermal conductance of tissues was first estimated in 1911, by Lefevre.[13] Hill[14] has published excellent studies on the measurement of heat loss, at body temperature, by radiation, convection, and evaporation. More recently, Cobet and Bramigk,[15] and, later still, Bedford and Warner[16] and Bedford[17] have used radiometers in the measurement of skin temperature and the study of heat loss. Bohnenkamp[18, 19] was the first to emphasize the importance of the profile, or effective, radiation surface, which, he found, amounted to approximately 80 per cent of the total body surface. Using an ingeniously constructed jacket of resistance wires, Burton[20, 21] recorded the changes in skin temperature brought about by a measured amount of work. Later, Burton and Murlin,[22] working with a calorimeter and a Burton resistance jacket, gathered data relating to surface area and temperature gradients. Winslow, Herrington, and Gagge[23-26] have made an analysis of all of the physical factors concerning heat loss under a wide variety of environmental conditions; they found large differences between the

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relative proportions of radiation and convection. Their work developed the study of the thermal conductance of the skin. From changes in thermal conductance they calculated the depth of the thermal gradient of the body and measured the peripheral circulation. Using these principles, Hick, Keeton, Glickman, and Wall[27] made studies of normal persons under varying environmental conditions, and calculated an index to peripheral circulation, blood volume, and cardiac output. Burton and Bazett,[28] Bazett,[29] and Bazett and McGlone,[30, 31] have also made fundamental contributions relating to the temperature of the subcutaneous tissues and muscles and the temperature gradients.

CALCULATIONS

A formula has been devised by Hardy and Soderstrom[32] to express the internal thermal exchanges of the body in terms of total blood flow to the skin in cubic centimeters per minute. If the internal (or rectal) temperature, the heat eliminated (that is to say, heat loss), and the average weighted skin temperature are measured, the relative flow of blood to the peripheral tissues may be calculated. Their technique was modified by Stewart and Jack[33] so that average weighted skin temperature, rectal temperature, and basal metabolic rate could be used in the estimation of peripheral blood flow. This modified technique has been followed in our investigations.

With increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface, so that the thermal conductance of the superficial tissues is increased. Therefore, changes in thermal conductance become an index to peripheral blood flow.

The formula for calculating peripheral blood flow is as follows:[32]

$$\text{I.} \qquad F = 17 \times A \left(\frac{Hl}{MR - MS} \overset{♂}{-9.1}\ \overset{♀}{[-6.5]}\right)$$

in which,

F = peripheral conductance above minimal value
17 = factor for converting Cal./C°/M²/Hr. into c.c./min.
A = surface area in sq. meters
Hl = heat loss (for calculation, see Formula II)
MR = mean rectal temperature
MS = mean of average skin temperature
9.1 = kilocals/C°/M²/Hr. (Average thermal conductivity of superficial tissue with minimum blood flow for males in temperatures below 28° C.[32])
6.5 = same as above for females[32]

"F" in this formula measures the heat carried to the surface in excess of heat conducted by the tissues; therefore, it can be taken as a positive index of the volume of blood circulating in the periphery. If blood enters the periphery at rectal temperature and finally reaches the skin at skin temperature, then "F" will measure this flow in cubic centimeters per minute.

In order to use this formula in our observations, it was necessary to compute heat loss (Hl) from the sum of heat produced (Hp) and heat storage (Hs).

II. $Hl = (Hp) + (Hs)$
in which,
Hl = heat loss
Hp = heat produced (calculated from oxygen consumption)
Hs = heat storage (for calculation, see Formula III)
Heat storage is calculated from the following formula:

III. $Hs = W \times 0.8 \, [(\Delta R \times 0.8) + (\Delta S \times 0.2)]$
in which,
Hs = heat storage
W = body weight in kilograms
0.8 = average specific heat of body tissues
$\Delta R \times 0.8$ = weighted change in rectal temperature
$\Delta S \times 0.2$ = weighted change in average skin temperature

IV. $\Delta R = R_B - R_E$
in which,
ΔR = change in rectal temperature
R_B = rectal temperature at beginning of twenty-minute period
R_E = rectal temperature at end of twenty-minute period

V. $\Delta S = S_B - S_E$
in which,
ΔS = change in average skin temperature
S_B = average skin temperature at beginning of twenty-minute period
S_E = average skin temperature at end of twenty-minute period

Winslow, Herrington, and Gagge[24] have considered heat storage as "positive" or "negative." Using their terminology, positive values for storage correspond to a cooling of the body, and negative values, to a heating of the body. In short, when the temperature falls (see rectal temperatures, pages 721 and 722), "positive storage" occurs, and when the temperature rises (see skin temperatures, pages 721 and 722), "negative storage" occurs. It will be seen later, in the section on example of calculations (pages 721 and 722), that, for the first twenty-minute period "during iodine," in the case of A. S.[I], "negative storage" occurred. Formulas IV and V are based on these principles.

Formula III represents the change in average, weighted, body temperature from one set of rectal and skin temperature readings to the next, multiplied by the body weight and average specific heat of body tissues. From a series of six sets of readings during a morning's observations, we were able to calculate the heat storage (Hs) for five average periods. Substituting the sum of heat produced (Hp) and heat storage (Hs) for heat loss (Hl) into Formula I, the peripheral blood flow was calculated in c.c. per minute for each of the five periods. We have divided this value by the surface area in square meters, in order to express the peripheral blood flow in cubic centimeters per sq. m. per minute (see example of calculation on page 721).

It may be pointed out that Burton,[20, 21] Burton and Murlin,[22] Winslow, Herrington, and Gagge,[23, 24] Du Bois,[34] and Hardy, Du Bois, and Soderstrom[35] have measured heat loss by the method we have employed (Formula II), and compared it with actual measurements of heat loss by direct calorimetry; they obtained results of sufficient accuracy for the purposes of this investigation.

It has been estimated from direct calorimetry[35] that weighting the rectal temperature 80 per cent (0.8 in Formula III), and the skin temperature 20 per cent (0.2 in Formula III), gives an approximation of the average body temperature. Using a different method, Burton[36] arrived at values of 65 and 35 per cent, respectively. All agree that using surface temperatures gives a greater degree of accuracy in calculating the average body temperature, and, although rectal temperature has the larger coefficient, the surface temperature is the more important because it changes more in short periods. Hardy, Du Bois, and Soderstrom[35] have pointed out that approximately two tenths of the body mass lies within 1 cm. of the skin surface. Winslow, Herrington, and Gagge[37] have found that the average temperature gradient extends 2.2 cm. below the surface. Hardy, Du Bois, and Soderstrom[35] estimated that this gradient was 2.0 cm. Allotment of a weighting of 20 per cent of skin temperature arises from several independent sources. The values for weighting average body temperature and the temperature gradient derived by Hardy, Du Bois, and Soderstrom[35] have been used in our studies.

The improved radiometer devised by Hardy and Soderstrom[38] was employed to record skin temperatures. It is very accurate and rapid, and, by a critical comparison,[39] it now appears to be the best method for securing absolute measurements of skin temperature. Hardy and Muschenheim[40] have demonstrated that, from the standpoint of human radiation, a "perfect black body" is a substance which reflects and transmits none of the far infrared rays, but absorbs them all; or, if heat is traveling in the opposite direction, radiates them all. The validity of measurements of skin temperature by the radiometric method has been upheld by the work of Hardy,[41, 42] Hardy and Muschenheim,[40] and Hardy and Oppel.[43] These investigations show that the human skin is practically a perfect, infrared, "black-body" radiator. Moreover, they have shown that, at the temperature of the human body, the emissions of infrared rays fall between 5μ and 20μ, and that, in this range, there is essentially no difference in the emissivity of the skins of white men and negroes. The "blackness" of the skin is of considerable physiologic importance, for it enables the investigator to calculate skin temperature from radiation.[34] The human skin is slightly more efficient as an insulator than cork;[13, 40, 43] when one lies nude and motionless in the basal state, with the environmental temperature below 28° C., it functions like a dead insulator and is practically bloodless,[42] and the blood flow to the skin, the thermal conductivity of the peripheral tissues, and vaporization are constant.[32, 42] Hardy and Soderstrom[32] have found that the average thermal conductivity of superficial tissues, when blood flow is minimal, is approximately 9.1 kilocals/C°/M^2/Hr. for men, and about 6.5 for women (Formula I). These values remain almost constant when the room temperature is below 28° C. However, it is well

known that, for persons with more than the average amount of subcutaneous fat, these values may be too high.

METHODS

In order to measure the peripheral blood flow according to the method devised by Hardy and Soderstrom[32] (Formula I), it was necessary to secure certain data, namely, recordings of skin and of rectal temperatures, of oxygen consumption, of height, and of body weight. In addition, observations were made on blood pressure, arm-to-tongue circulation time, and pulse rate.

The room in which our studies were carried out was small and compact; it had one small door, one window, and a steam radiator. The humidity was not measured; since most of the observations were made during the winter months, and because of the steam radiator, it must necessarily have been low. Heat loss from convection was kept at a minimum by placing a metal screen in front of the window. Patients lying flat in bed perspire in those parts which are in contact with the mattress. It was impossible to prevent this. (In the Russell Sage calorimeter, in which subjects lie on a bed made of heavy fishing line, this factor, as well as conduction, is eliminated.) Under our environmental conditions, however, conduction and vaporization were reduced to a minimum, for the room temperature was kept within the cool zone of approximately 23° to 27° C. Close attention to the door, window, and radiator enabled us to keep the temperature of the room constant within ± 0.5° C. during all observations on any patient. The observations on one of the earlier patients were discarded because the room temperature during the three periods of investigation showed too great variation.

Skin temperatures were measured at eleven points of uniform area on the anterior surface of the body (Fig. 1), using a Hardy-Soderstrom radiometer[38] which was calibrated to read directly in degrees centigrade on a galvanometer scale. These skin temperatures were weighted according to the surface of the body which they represented (Hardy, et al.,[35] p. 466) (Fig. 1).

Rectal temperatures were measured by means of a single-junction thermocouple,[38] one end of which was immersed in a pint thermos flask filled with warm water kept at body temperature; the other end, which was silver-tipped, was inserted into the rectum for approximately 10 cm. as soon as the patient came to the room, and remained in place throughout the morning. The connections were arranged so that readings could be made from the galvanometer scale of the radiometer, which was calibrated to show degrees centigrade directly. The readings are accurate to ± 0.02° C.[38, 39]

Oxygen consumption was measured with a Benedict-Roth metabolism apparatus.[44] The basal metabolic rate was calculated from the Mayo Foundation Standards for age and sex,[45] and the surface area was estimated from the tables of Du Bois and Du Bois.[46]

Blood pressures were measured with a standard mercury sphygmomanometer, and in accordance with the joint recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland.[47]

The arm-to-tongue circulation time was measured by means of decholin;[7] 5 c.c. of a 20 per cent solution were injected rapidly (one to two seconds) through an 18-gauge needle into an antecubital vein while the subject was lying quietly in the supine position. This was repeated in one and one-half minutes. The time was recorded from the beginning of the injection until the subject first perceived the bitter taste.

PROCEDURE

The procedure was similar for all patients. Most of them were in the hospital several days before the first studies were made. During this time they became

accustomed to hospital routine, but were not trained for the procedures. Since one of the characteristics of Graves' disease is emotional instability, all of the patients were assured that the procedures would have no harmful effect. The use of the radiometer and our plan of investigation were outlined to each. During the various phases of our study all of the subjects cooperated well.

All of the observations were made in the morning, when the patients were in a basal metabolic state. The patients, lying nude in bed with the rectal thermometer in place, were covered only by a sheet. During the first hour, when the subjects were adjusting to the environment, no observations were made.

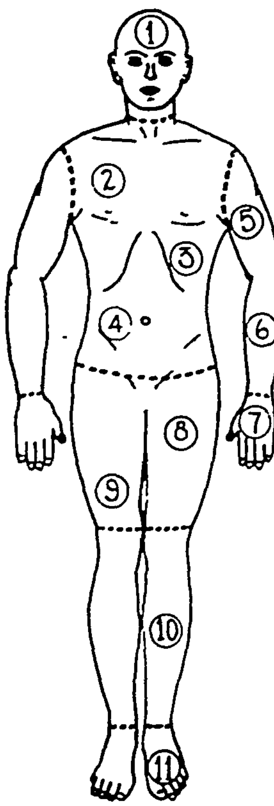

Fig. 1.—This figure shows the locations of eleven areas over the anterior surface of the body where skin temperatures were measured with the Hardy-Soderstrom radiometer. Weightings for the divisions of body surface, totaling 1.00, are: Head, *1*, = 0.07; trunk, *2*, *3*, *4*, = 0.35; arms, *5*, *6*, = 0.14; hands, *7*, = 0.05; thighs, *8*, *9*, = 0.19; legs, *10*, = 0.13; and feet, *11*, = 0.07. (Hardy and Du Bois,[35] p. 466.) The sum of the weighted temperature of each area equals the average skin temperature:

$$[(T_1 \times 0.07) + (\frac{T_2 + T_3 + T_4}{3} \times 0.35) + (\frac{T_5 + T_6}{2} \times 0.14) + (T_7 \times 0.05) + (\frac{T_8 + T_9}{2} \times 0.19) + (T_{10} \times 0.13) + (T_{11} \times 0.07)] = S.$$

The order in which data were collected was as follows: First, the oxygen consumption was measured. The room temperature was then noted, after which the temperatures of the skin of the eleven areas (Fig. 1) were recorded. The rectal temperature was then measured. The same procedure was repeated, at intervals of twenty minutes, until a series of six separate readings had been obtained; from these the peripheral blood flow was calculated for five average periods. The blood pressure was measured and the pulse rate counted during free intervals. After completing the recordings of skin and rectal temperatures, the oxygen consumption was measured again, followed by estimations of the arm-to-tongue circulation time. Subsequent studies were made in exactly the same sequence "during iodine" and "after operation," and the environmental conditions were duplicated as nearly as possible. Throughout this paper the terms "before iodine," "during iodine," and "after operation" are used to indicate that these patients were first studied before the institution of iodine therapy, while receiving iodine,

usually one to two days before operation, and in the latter part of their convalescence from subtotal thyroidectomy, respectively.

EXAMPLE OF THE CALCULATION OF PERIPHERAL BLOOD FLOW

The following data were obtained in the case of patient A. S.[I] during the first two periods of observation "during iodine" (Fig. 2). By using these data in the appropriate formulas (pages 716 and 717), peripheral blood flow for the first twenty-minute period is calculated as follows:

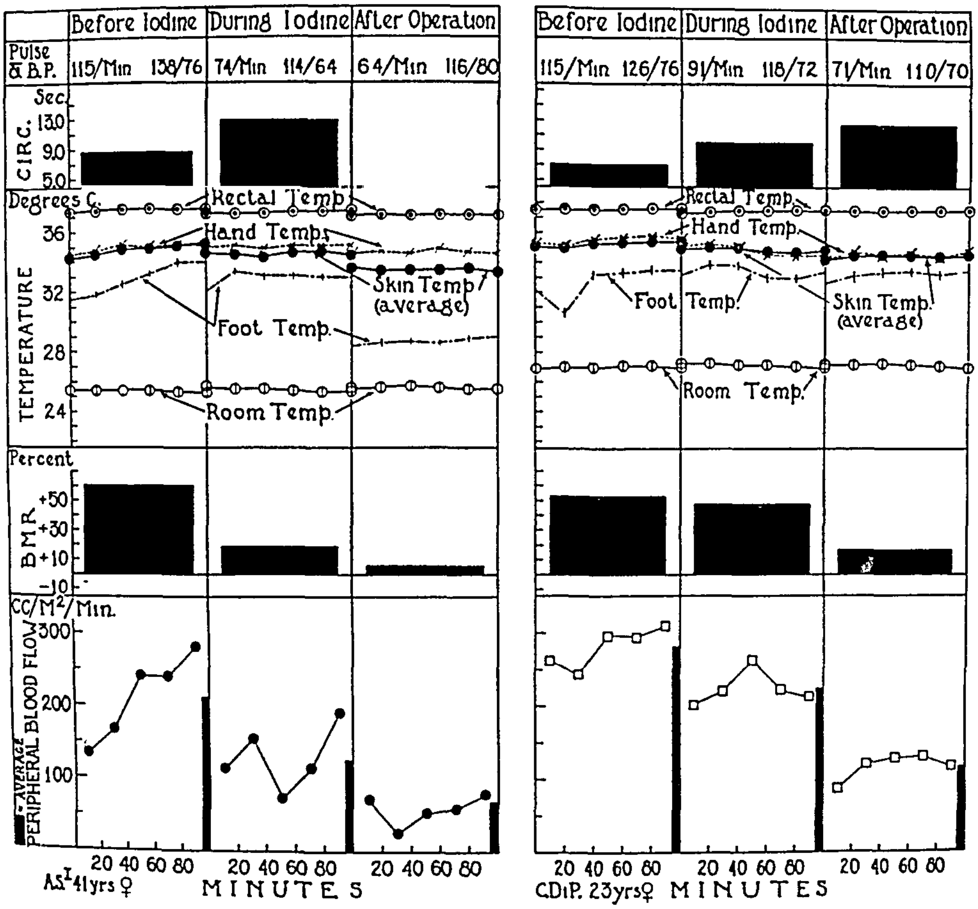

Fig. 2.—In this figure there are plotted data relating to patients A. S.[1] and C. DiP. to show the effect of room temperature on peripheral blood flow. Average peripheral blood flow is indicated by the solid column at the end of each phase. "Before iodine," the peripheral blood flow was less in patient A. S.[1] than in patient C. DiP. at the higher room temperature. There was only a rough correlation between the temperature of the hands and feet and average skin temperature; this was particularly the case with respect to the feet.

The average skin temperature (p. 722, column 4) was derived by weighting the skin temperatures of the eleven areas shown in Fig. 1 (Hardy, et al.,[35] p. 466). For example, the average skin temperature at the beginning of the first twenty-minute period was calculated in the following manner:

$$S_B = [(T_1 \times 0.07) + (\frac{T_2 + T_3 + T_4}{3} \times 0.35) + (\frac{T_5 + T_6}{2} \times 0.14) + (T_7 \times 0.05) + (\frac{T_8 + T_9}{2} \times 0.19) + (T_{10} \times 0.13) + (T_{11} \times 0.07)] = [(35.4 \times 0.07) + (\frac{35.0 + 35.7 + 34.9}{3} \times 0.35) + (\frac{33.2 + 34.1}{2} \times 0.14) + (35.0 \times 0.05) + (\frac{33.7 + 32.7}{2} \times 0.19) + (33.2 \times 0.13) + (32.0 \times 0.07)] = 34.13° \text{ C.}$$

(See p. 722.)

The average skin temperature at end of twenty-minute period S_E was calculated in a similar manner.

Name: A. S.[I]			Sex: Female			Total heat production, from oxygen consumption, 75.7 cal./hr.								
Age: 41 years			B.M.R. +18 per cent			Total surface area, 1.80 sq.m. = A								
Height: 166.0 cm.														
Weight: 71.1 kg.														
Time (A.M.)	Room Temperature (°C.)	Rectal Temperature (°C.) = R (p. 723)	Average Skin Temperature (°C.) = S (p. 721)	Skin Temperature (Radiometer) from Areas Shown in Fig. 1 = T										
				T_1 (°C.)	T_2 (°C.)	T_3 (°C.)	T_4 (°C.)	T_5 (°C.)	T_6 (°C.)	T_7 (°C.)	T_8 (°C.)	T_9 (°C.)	T_{10} (°C.)	T_{11} (°C.)
10:10	25.6	$37.28 = R_B$	$34.13 = S_B$	35.4	35.0	35.7	34.9	33.2	34.1	35.0	33.7	32.7	33.2	32.0
10:30	25.5	$37.23 = R_E$	$34.49 = S_E$	35.2	35.2	35.7	35.2	33.6	34.2	35.2	34.5	33.5	33.1	33.7

The rectal temperatures at the beginning (R_B) and the end (R_E) of the first twenty-minute period were 37.28° C. and 37.23° C., respectively. The average skin temperatures at the beginning (S_B) and the end (S_E) were 34.13° C. and 34.49° C., respectively.

Substituting in Formula IV,

$$\begin{aligned} \triangle R &= R_B - R_E \\ &= 37.28° \text{ C.} - 37.23° \text{ C.} \\ &= +0.05° \text{ C.} \end{aligned}$$

Likewise, substituting in Formula V,

$$\begin{aligned} \triangle S &= S_B - S_E \\ &= 34.13° \text{ C.} - 34.49° \text{ C.} \\ &= -0.36° \text{ C.} \end{aligned}$$

Substitute the values derived by Formulas IV and V into Formula III for the calculation of heat storage (Hs).

$$\begin{aligned} Hs &= W \times 0.8\,[(\triangle R \times 0.8) + (\triangle S \times 0.2)] \\ Hs &= 71.1 \times 0.8\,[(+0.05 \times 0.8) + (-0.36 \times 0.2)] \\ &= 56.9\,[(+0.040) + (-0.072)] \\ &= 56.9\,(-0.032) \\ &= -1.82 \text{ cal./20 min.} \end{aligned}$$

Since -1.82 cal. is the heat storage for a twenty-minute period, to derive the heat storage for one hour, multiply by 3:

$$\begin{aligned} Hs &= 3 \times (-1.82 \text{ cal.}) \\ &= -5.46 \text{ cal./hr.} \end{aligned}$$

Referring to Formula II,

$$\begin{aligned} Hl &= (Hp) + (Hs) \\ &= (75.70 \text{ cal./hr.}) + (-5.46 \text{ cal./hr.}) \\ &= 70.24 \text{ cal./hr.} \end{aligned}$$

To reduce to cal./sq.m./hr., divide by surface area (1.80 sq.m.):

$$\begin{aligned} Hl &= \frac{70.24 \text{ cal./hr.}}{1.80 \text{ sq.m.}} \\ &= 39.0 \text{ cal./sq.m./hr.} \end{aligned}$$

Calculations of the mean rectal and the mean of the average skin temperatures (MR and MS, respectively, in Formula I) for the first twenty-minute period were as follows:

$$\begin{aligned} \text{VI.}\quad MR &= \frac{R_B + R_E}{2} \\ &= \frac{37.28° \text{ C.} + 37.23° \text{ C.}}{2} \\ &= 37.26° \text{ C.} \end{aligned}$$

and,

$$\begin{aligned} \text{VII.}\quad MS &= \frac{S_B + S_E}{2} \\ &= \frac{34.13° \text{ C.} + 34.49° \text{ C.}}{2} \\ &= 34.31° \text{ C.} \end{aligned}$$

As a final step, substitute the values for heat loss (Hl), the mean rectal temperature (MR), and the mean of the average skin temperature (MS) into Formula I, using -6.5 as the average thermal conductivity for females:

$$\begin{aligned} F &= 17 \times A\left(\frac{Hl}{MR - MS} - 6.5\ ♀\right) \\ &= 17 \times 1.80\left(\frac{39.0}{37.26 - 34.31} - 6.5\right) \\ &= 30.6\left(\frac{39.0}{2.95} - 6.5\right) \\ &= 30.6\,(13.2 - 6.5) \\ &= 30.6 \times 6.7 \\ &= 205 \text{ c.c./min.} \end{aligned}$$

Reducing the blood flow to c.c./sq.m./min., since the surface area was known,

$$F = \frac{205 \text{ c.c./min.}}{1.80 \text{ sq.m.}}$$
$$= 114 \text{ c.c./sq.m./min.},$$

which was the average peripheral blood flow for the first twenty-minute period "during iodine" (Fig. 2).

Peripheral blood flow, as we have calculated it, is an expression of the average of total peripheral response to changes in the vascular tree, and is a measure of the total amount of blood allocated to the periphery of the whole body, or to each square meter of body surface when this is divided by the surface area. The result is expressed in cubic centimeters per square meter per minute. We are of the opinion that a much more accurate index of peripheral circulation is obtained by this means than by estimations of circulation in an isolated extremity or digit by recording its skin temperature or its changes in volume. The temperature of the hands and feet is deceptive, as was pointed out by Du Bois.[34] Our observations confirm this; therefore, the conception of peripheral blood flow as an average total surface function appears to be the proper approach to this problem.

OBSERVATIONS

Peripheral Blood Flow and Basal Metabolic Rate.—"Before iodine," the highest, lowest, and *average* basal metabolic rates were +83, +21, and *+45* per cent, respectively; and the highest, lowest, and *average* peripheral blood flows were 235, 134, and *182* c.c. per square meter per minute, respectively (Figs. 3 and 4) (Table I). In short, in the "before iodine" phase, when the basal metabolic rate was high, the peripheral blood flow was also elevated.

Table I

Average Values of Data Relating to Eighteen Patients With Hyperthyroidism

	BEFORE IODINE	DURING IODINE	AFTER OPERATION
Basal metabolic rate	45%	23%	9%
Peripheral blood flow	182 c.c./M²/min.	109 c.c./M²/min.	55 c.c./M²/min.
Skin temperature	34.58° C.	33.58° C.	33.08° C.
Temperature of hands	34.7° C.	34.0° C.	34.0° C.
Temperature of feet	32.4° C.	31.0° C.	29.7° C.
Rectal temperature	37.32° C.	37.24° C.	37.28° C.
Circulation time	9.1 sec.	10.2 sec.	12.6 sec.
Pulse rate	104/min.	86/min.	81/min.
Pulse pressure	58 mm. Hg	47 mm. Hg	43 mm. Hg
Peripheral resistance	.74 mm. Hg/c.c./M²/min.	1.34 mm. Hg/c.c./M²/min.	3.12 mm. Hg/c.c./M²/min.

"During iodine," the highest, lowest, and *average* basal metabolic rates were +48, +5, and *+23* per cent, respectively; and the highest, lowest, and *average* peripheral blood flows were 225, 50 and *109* c.c. per square meter per minute, respectively. All patients "during iodine" showed a fall in basal metabolic rate and peripheral blood flow.

"After operation," the highest, lowest, and *average* basal metabolic rates were +19, +3, and *+9* per cent, respectively; and the highest, lowest,

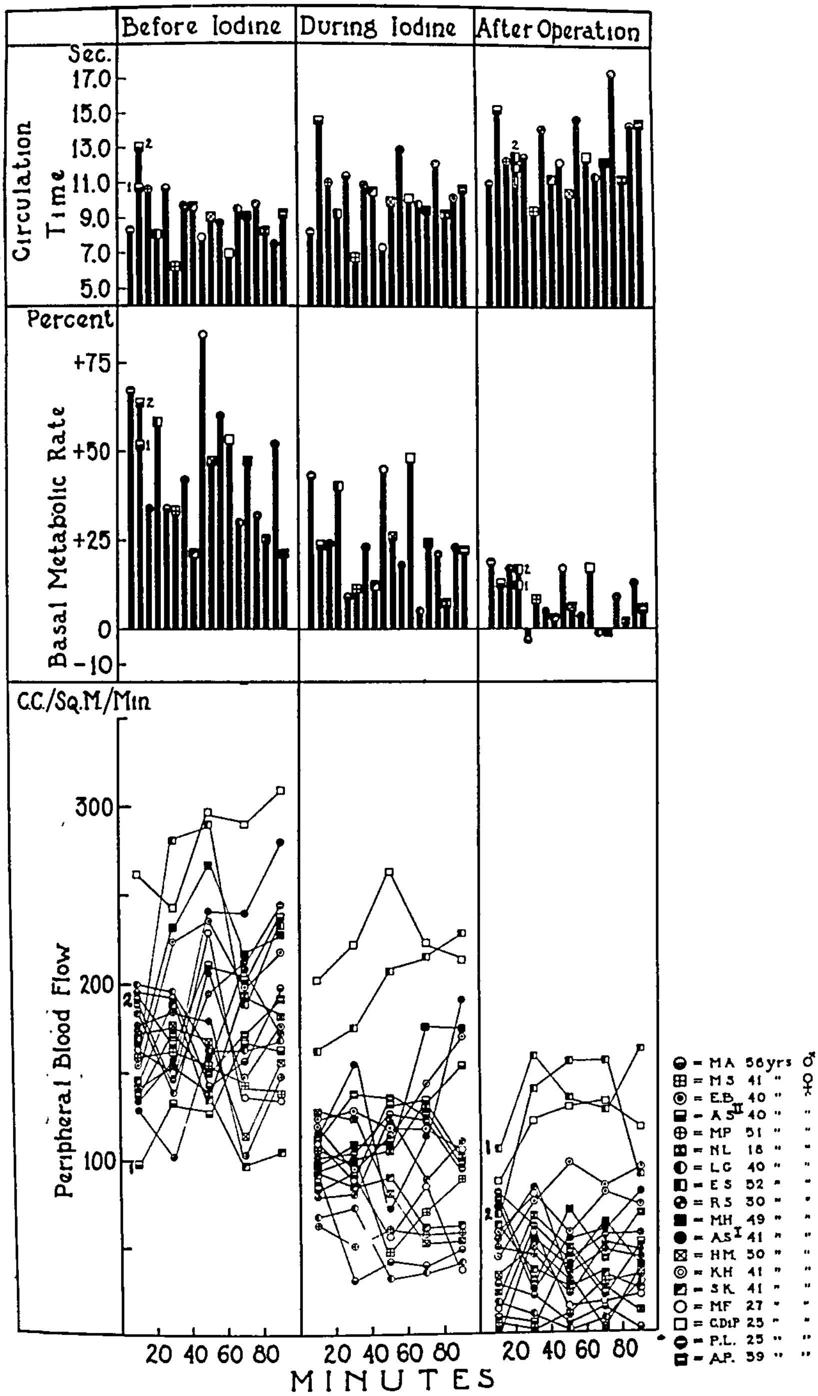

Fig. 3.—In this figure there are plotted for all patients the peripheral blood flow, basal metabolic rate, and circulation time "before iodine," "during iodine," and "after operation." Each patient is indicated by a symbol. In the case of A. S.[11], who had auricular fibrillation "before iodine," studies were made before, and again after, digitalization (indicated by *1* and *2*, respectively). Because patient E. S. was subjected to a two-stage subtotal thyroidectomy, observations were made on two occasions "after operation" (indicated by *1* and *2*, respectively).

and *average* peripheral blood flows were 137, 9, and *55* c.c. per square meter per minute, respectively. Finally, further decreases in basal metabolic rate and peripheral blood flow were observed "after operation." It may be recalled that Hardy and Soderstrom[32] found in normal subjects that the average peripheral blood flow was 15 c.c. per square meter per minute at temperatures below 28° C.

Average Skin Temperature.—"Before iodine," the highest, lowest, and *average* skin temperatures were 35.24° C., 32.97° C., and *34.58°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* skin temperatures were 34.90° C., 31.67° C., and *33.58°* C., respectively. "After operation," the highest, lowest, and *average* skin temperatures were 34.52° C., 30.53° C., and *33.08°* C., respectively. The skin temperature, therefore, continued to decrease through the period of iodine therapy and after operation.

Temperature of the Hands and Feet.—"Before iodine," the highest, lowest, and *average* temperatures of the hands were 35.5° C., 31.4° C., and *34.7°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* temperatures of the hands were 35.4° C., 32.2° C., and *34.0°* C., respectively. "After operation," the highest, lowest, and *average* temperatures of the hands were 35.3° C., 32.7° C., and *34.0°* C., respectively.

"Before iodine," the highest, lowest, and *average* temperatures of the feet were 34.6° C., 22.1° C., and *32.4°* C., respectively (Table I). "During iodine," the highest, lowest, and *average* temperatures of the feet were 33.8° C., 24.6° C., and *31.0°* C., respectively. "After operation," the highest, lowest, and *average* temperatures of the feet were 33.3° C., 25.0° C., and *29.7°* C., respectively.

Rectal Temperature.—The rectal temperature showed no significant changes. The greatest range of change in any one subject during the various periods of observations was ±0.25° C., as, for example, in patient A. S.^{I} (Fig. 2). A single exception will be discussed later (page 731, A. S.^{II}). The average rectal temperature for the group "before iodine" was 37.32° C., "during iodine," 37.24° C., and "after operation," 37.28° C. (Table I).

The temperatures of the hands were, in most instances, in a zone between average skin temperature and rectal temperature, whereas the temperatures of the feet usually fluctuated between average skin temperature and room temperature.

Circulation Time.—"Before iodine," the circulation time was short; the *average* was *9.1* sec. for the group (Fig. 4) (Table I). The shortest during this period was 6.0 sec., and the longest, 13 sec. (Fig. 3). "During iodine," the *average* circulation time for all patients was *10.2* sec., the shortest, 6.8 sec., and the longest, 14.5 sec. "After operation," the *average* circulation time for the group was *12.6* sec., the shortest, 9.4 sec., and the longest, 17.4 sec. In short, a definite but not striking

increase in circulation time occurred during treatment with iodine, and the time approached normal after operation.

Pulse Rate.—The *average* pulse rate was *104* per minute "before iodine"; the highest was 115 per minute, and the lowest, 87 per minute (Table I). "During iodine," the *average* pulse rate was *86* per minute, the highest, 119 per minute, and the lowest, 70 per minute. "After operation," the *average* pulse rate was *81* per minute, the highest, 100 per minute, and the lowest, 64 per minute. The pulse rates in all cases showed decreases which ran parallel with the fall in basal metabolic rate and peripheral blood flow.

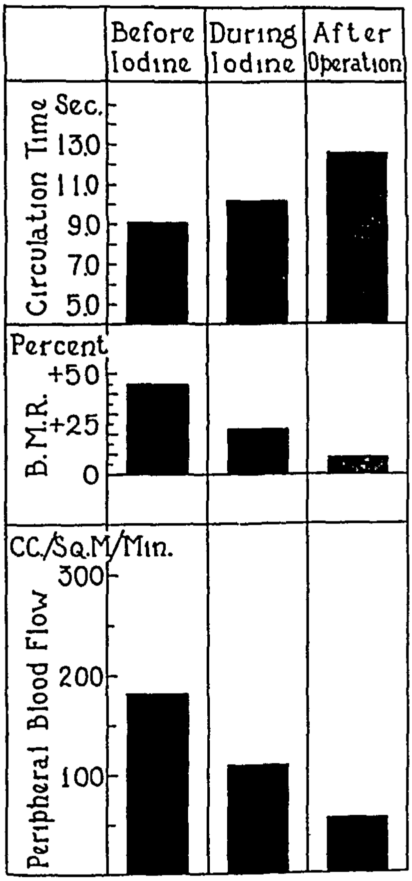

Fig. 4.—In this figure there are plotted the average peripheral blood flow, average basal metabolic rate, and average circulation time for the eighteen patients.

Pulse Pressure.—The pulse pressure was relatively large "before iodine" in all but two cases. The *average* was *58* mm. Hg (Table I). It fell to *47* mm. Hg "during iodine," and to *43* mm. Hg "after operation." The highest recorded "before iodine" was 81 mm. Hg, and the lowest, 35 mm. Hg. The highest "during iodine" was 68 mm. Hg, and the lowest, 30 mm. Hg. "After operation," the highest was 75 mm. Hg, and the lowest, 26 mm. Hg.

Peripheral Resistance.—Since the flushed appearance of these patients suggests peripheral vasodilatation, an estimation of peripheral resis-

tance during the various stages was made. The average systolic blood pressure, in millimeters of mercury, for each experimental period of observation was divided by the average blood flow in cubic centimeters per square meter per minute. The result was expressed as the pressure, in mm. Hg, which was required to force 1 c.c. of blood through 1 sq. m. of skin surface per minute. The *average* pressure required "before iodine" was 0.74 mm. Hg; "during iodine" it rose to 1.34 mm. Hg, and "after operation" to 3.12 mm. Hg per cubic centimeter per square meter per minute (Table I).

DISCUSSION

In every case, the peripheral blood flow was large at first, at a time when the basal metabolic rate was increased. The flow diminished after giving iodine, when the basal metabolic rate had decreased, and this was followed by a still further decrease in flow and fall in basal metabolic rate after subtotal thyroidectomy. Moreover, when the data for all patients were pooled and blood flow was plotted against basal metabolic rate, a linear relationship was revealed (Fig. 5); high basal metabolic rates were associated with an increase in peripheral blood flow, and a progressive decrease in peripheral blood flow occurred with the decrease in basal metabolic rate.

In the period "before iodine," and again "during iodine," the wide fluctuations in peripheral blood flow (Fig. 3) were interpreted as evidence of vasomotor instability. Clinically, it was apparent during the course of a morning's observations that the flushing of the skin became deeper at times, as if the peripheral vascular tree were undergoing intermittent periods of increased vasodilatation. "After operation," fluctuations in peripheral blood flow were less marked (Fig. 3).

The scattering of peripheral blood flow at various levels among individual patients during the three stages of study (Fig. 3) was caused partly by differences in basal metabolic rate, and partly by differences in room temperature. Hick, Keeton, Glickman, and Wall[27] showed that blood flow to the periphery increased as the environmental temperature increased. Certain of our data point to the same conclusion. To illustrate this point, we have plotted the data for two patients so that they may be compared (Fig. 2). The room temperature during observations on patient A. S.[1] remained near 25.5° C., whereas, in the case of patient C. DiP., it was approximately 1.5° C. higher. Although the basal metabolic rate, pulse rate, and pulse pressure were approximately the same "before iodine," the average blood flow was 69 c.c. per square meter per minute greater in the case of C. DiP. at the higher room temperature. The average skin temperature usually showed a similar response to room temperature. This was only roughly true, however, of the temperature of the hands and feet. It was because of the important role played by environmental temperature on blood flow that care was exercised to carry out all observations on any one patient at approximately the same room temperature.

The skin of these thyrotoxic patients appeared hot and flushed when they were first seen, even under basal conditions. This indicated an increase in average skin temperature and peripheral blood flow. Our objective data confirm this clinical impression. "Before iodine," the average skin temperature and peripheral blood flow were elevated at a time when the basal metabolic rate was high, and with the decrease in basal metabolic rate "during iodine," and again "after operation," there was a progressive and parallel decrease in average skin temperature and peripheral blood flow.

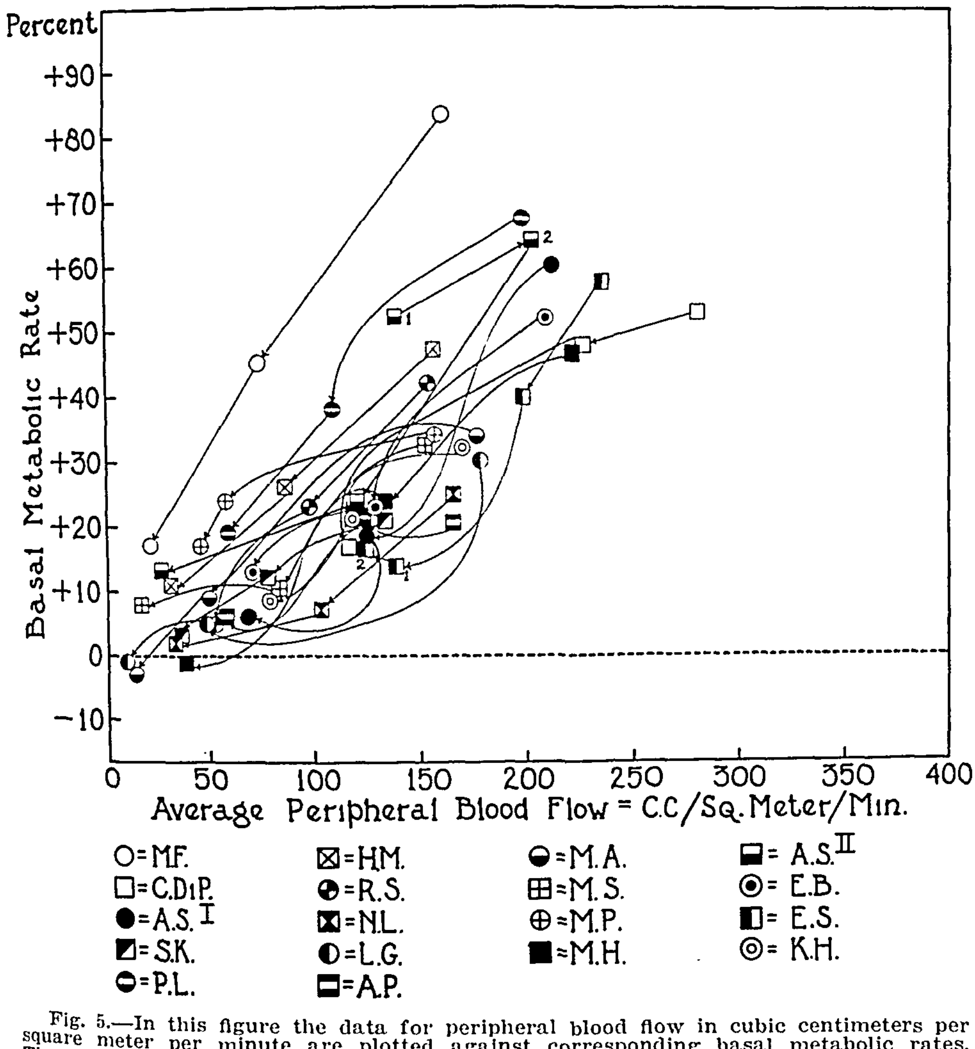

Fig. 5.—In this figure the data for peripheral blood flow in cubic centimeters per square meter per minute are plotted against corresponding basal metabolic rates. The symbols for each patient are connected by arrows to aid in following each patient through the various phases. There is a linear relationship, for, with a decrease in basal metabolic rate, the peripheral blood flow also decreased.

There was no correlation between the temperature of the hands and feet and average skin temperature (Fig. 2). The average temperature of the hands was higher in all instances than average skin temperature. Between the first and second periods of observation, average skin temperature fell 1.0° C., while the temperature of the hands decreased 0.68°

C. Comparison of the periods "during iodine" and "after operation" showed that average skin temperature decreased 0.50° C., but that of the hands decreased only 0.05° C. For the most part, however, the temperature of the hands followed more closely the changes in average skin temperature than did the temperature of the feet (Fig. 2). The temperature of the feet was approximately 2.0° C. to 4.0° C. below average skin temperature, underwent more rapid and wider fluctuations than that of the hands (Fig. 2), and was, at times, below room temperature when this was approximately 23.0° C. It is known that the temperature of the hands and feet is extremely labile. Moreover, the palmar and plantar surfaces perspire freely. The temperatures of the dorsal surface of the hand and the extensor surface of the foot were recorded, therefore, in order to eliminate, as far as possible, the effects of perspiration on skin temperature. Mittelmann and Wolff[48] have shown that the hands respond rapidly and widely to emotion. Du Bois[34] found that the feet cooled too rapidly. Because of these factors, it appears to us that the estimation of peripheral blood flow by measuring skin temperatures or volume changes of an extremity or digit would often be not only a very rough index of peripheral blood flow, but frequently a misleading index. We emphasize again that we measure average peripheral blood flow for the whole surface area. Although there may be general vasodilatation, there may be, at the same time, very marked local vasoconstriction; this occurs, as Hardy* has shown, after giving adrenalin.

The rectal temperature showed a remarkable constancy. "During iodine" the average temperature was 0.08° C. lower than "before iodine." "After operation" there was a rise of 0.04° C. The change, therefore, from the time the patients were first seen until after subtotal thyroidectomy was only 0.04° C. It may be recalled that the average change in skin temperature between the first and second periods was 1.00° C., and that a further decrease of 0.50° C. occurred between the second and third periods, making a total decrease of 1.5° C. This emphasizes a point which was made earlier, namely, that, although the rectal temperature has the larger weighting (80 per cent), the changes in weighted skin temperature (20 per cent) are more important in the estimation of peripheral blood flow.

Two of the patients require discussion because four sets of observations were made, instead of three.

Patient E. S. (History No. 100740), because of her age and of marked thyrotoxicosis, was subjected to a two-stage operation. "Before iodine," the basal metabolic rate was +58 per cent, and the average peripheral blood flow, 235 c.c. per square meter per minute. A decrease of basal metabolic rate to + 40 per cent, and of peripheral blood flow to 198 c.c. per square meter per minute, took place "during iodine." Following removal of the right lobe of the thyroid on Feb. 27,

*Personal communication.

1940, the basal metabolic rate fell to +14 per cent and the peripheral blood flow to 137 c.c. per square meter per minute. Removal of the left lobe was performed March 11, 1940. Although the basal metabolic rate remained essentially the same (+17 per cent), further decrease in peripheral blood flow, to 123 c.c. per square meter per minute, occurred (Fig. 3). Moreover, this patient had the highest pulse rate of the group, not only "before iodine" (115 per minute), but also "after operation." On the first day after removal of the right lobe, the cardiac mechanism changed to auricular fibrillation. With the administration of digitalis, normal sinus rhythm recurred within thirty-six hours, and persisted. On the day of our observations, when the patient was under the influence of digitalis, her pulse rate was 99 per minute. With continuance of digitalis, during observations after removal of the left lobe, the pulse rate was 100 per minute. Average skin temperature, pulse pressure, peripheral resistance, and velocity and blood flow during the four periods showed changes, however, which were similar to those exhibited by the whole group.

In the case of patient A. S.[II] (History No. 260735), an extra set of observations was made "before iodine" because of the presence of auricular fibrillation. No signs of congestive heart failure were present. The basal metabolic rate, average peripheral blood flow, and circulation time were +52 per cent, 138 c.c. per square meter per minute, and 10.8 sec., respectively (Fig. 3). She was given digitalis, and the basal metabolic rate increased to +64 per cent; the average peripheral blood flow now measured 203 c.c. per square meter per minute, that is to say, it increased, and the circulation time was 13.0 sec. Maintenance doses of digitalis were continued, with the addition of iodine therapy. The basal metabolic rate fell to +24 per cent, the peripheral blood flow to 120 c.c. per square meter per minute, and the circulation time increased further to 14.5 sec. After subtotal thyroidectomy, the basal metabolic rate fell to +13 per cent, the peripheral blood flow to 26 c.c. per square meter per minute, and the circulation time increased still further, to 15.2 sec. The average rectal temperatures during the four periods of observation were 37.30° C., 37.81° C., 37.17° C., and 37.30° C., respectively. In short, there was a rise of 0.51° C. after digitalization, but before the institution of iodine therapy. The reason for the rise in rectal temperature in this patient requires consideration. Steele[49] concluded from a series of observations that elevation of rectal temperature may be brought about by obstruction to the peripheral circulation. In other studies he found that there was a rise in rectal temperature in patients with auricular fibrillation and heart failure.[50] The possibility of infection was eliminated in his cases. He attributed the elevation of rectal temperature to a deficiency in ability to lose heat, caused by slowing of the circulation. In our patient, the rise in rectal temperature was not brought about by peripheral circulatory obstruction, for the peripheral blood flow and average skin temperature

were increased at this time as a result of hyperthyroidism. With the disappearance of signs of heart failure, under digitalis therapy, the rectal temperature fell to normal in Steele's cases. Our subject showed no signs of heart failure, and, on digitalization, there was a sharp rise, not a fall, in rectal temperature. Between the first and second series of observations there was a rise of 12 per cent in basal metabolic rate and an increase in circulation time of 2.2 seconds. It has been shown by Stewart, Crane, Deitrick, and Thompson[51] that digitalis increases the work accomplished by the heart per beat, in relation to the cardiac size, whether the rhythm is normal or auricular fibrillation is present. We are of the opinion that the increase of 0.51° C. in average rectal temperature was caused by an excess of heat production over heat loss, in the amount of approximately 1 cal./hr. This was more than adequate to raise the rectal temperature 0.51° C. The increase in peripheral blood flow and average skin temperature after digitalization appears to have been caused by improvement in the general circulation in a patient whose tissue metabolism was increased as a consequence of hyperthyroidism.

The cardiac output is increased in thyrotoxicosis[2, 3, 4] and decreases with the administration of iodine, and again after subtotal thyroidectomy. We measured the cardiac output of one patient, A. S.[I] (History No. 230995), in order to correlate it with the peripheral blood flow. Because each of these procedures requires most of a morning, it was not possible to carry out both on the same day and still keep the patient under basal conditions. The volume output of the heart was therefore measured on the day following studies of peripheral blood flow. The patient was trained for this procedure beforehand. The cardiac output was estimated by the acetylene method; three samples of gas were taken, as recommended by Grollman,[52] and Grollman, Friedman, Clark, and Harrison.[53] The procedure was exactly the same as that which we followed on another occasion.[54] "Before iodine," at a time when the basal metabolic rate was +60 per cent and the peripheral blood flow 212 c.c. per square meter per minute, the cardiac output measured 3.48 liters per square meter per minute (arteriovenous oxygen difference, 54.6 c.c., oxygen consumption, 336 c.c. per minute, stroke volume, 61.5 c.c. per beat). "During iodine," at a time when the basal metabolic rate and peripheral blood flow were +18 per cent and 125 c.c. per square meter per minute, respectively, the cardiac output was 2.53 liters per square meter per minute (arteriovenous oxygen difference, 55.6 c.c., oxygen consumption, 251 c.c. per minute, stroke volume, 60 c.c. per beat). "After operation," when the basal metabolic rate was +6 per cent and the peripheral blood flow 69 c.c. per square meter per minute, the cardiac output was 2.02 liters per square meter per minute (arteriovenous oxygen difference, 57.7 c.c., oxygen consumption, 207 c.c. per minute, stroke volume, 53 c.c. per beat); these values were within the normal range. These data show that there was

an increased output of blood from the heart during the hyperthyroid stage which was adequate to supply the increased amount of blood allocated to the peripheral circulation.

The circulation time was recorded in order to correlate another factor, in addition to basal metabolic rate, with peripheral blood flow. When the basal metabolic rate and peripheral blood flow were elevated, the velocity of blood flow was increased. When these decreased during iodine therapy, and again after subtotal thyroidectomy, the velocity of blood flow also decreased in a parallel fashion (Fig. 4) (Table I).

There is a marked increase in oxygen requirements in hyperthyroidism. The organism attempts to provide this by increasing the volume output of blood.[2-4] Another compensatory measure may be the increase in circulating blood volume.[5, 6] The partition of the cardiac output to the various parts of the body in man is not known, although Levy and Blalock[55] have made some approximations in dogs. In hyperthyroidism, however, there is an ample increase in the total volume output of blood from the heart to provide for the increased amount of blood supplied to the periphery. Nevertheless, the heart is able to keep the blood moving at an increased velocity. We have shown that the peripheral resistance during this time is low. Boothby and Rynearson[4] have observed that in hyperthyroidism there is a greater increase in circulation rate than occurs in a normal subject as a result of a corresponding increase in oxygen consumption caused by work. They suggested that there might be a special circulatory stimulant in hyperthyroidism to account for this phenomenon; the observations of Stewart, Deitrick, and Crane[54] point to the absence of this factor in myxedema. There is also evidence for this possibility in the data herein reported. The decrease in peripheral blood flow, in cardiac output, and in the velocity of blood flow after subtotal thyroidectomy demonstrates that operation accomplishes something in the economy of the cardiovascular system which is not achieved by the use of iodine.

SUMMARY

This report concerns studies of the circulation in eighteen patients who were suffering from hyperthyroidism, with special reference to peripheral blood flow. A modification of the method of Hardy and Soderstrom was used to measure peripheral blood flow. The results may be summarized as follows:

1. The peripheral blood flow in c.c./M^2/min. was increased in hyperthyroidism at a time when the basal metabolic rate was elevated, decreased during iodine therapy, with a parallel fall in basal metabolic rate, and decreased still further after subtotal thyroidectomy.

2. There was a linear relationship between peripheral blood flow and basal metabolic rate in hyperthyroidism, in that, "during iodine" and "after operation," the fall in basal metabolic rate was associated with a decrease in peripheral blood flow.

3. In hyperthyroidism the peripheral resistance was low; it increased with iodine therapy, and increased still further after subtotal thyroidectomy. These changes were roughly in inverse ratio to the basal metabolic rate and peripheral blood flow.

4. The cardiac output, in the one case in which it was estimated before treatment, was increased, and showed changes parallel to those in basal metabolic rate and peripheral blood flow in the subsequent periods.

5. Velocity of blood flow, basal metabolic rate, and peripheral blood flow followed the same trend. When the basal metabolic rate and peripheral blood flow were high, the velocity of blood flow was increased. Under iodine therapy and after subtotal thyroidectomy, successive decreases in all occurred.

6. Average skin temperature, measured with a Hardy-Soderstrom radiometer, pulse rate, and pulse pressure followed roughly the fall in basal metabolic rate.

7. No direct relationship was observed between average skin temperature and the temperature of the hand and foot; this was particularly the case with respect to the foot.

PROTOCOLS

Since all of the patients had the typical signs and symptoms of hyperthyroidism, only short protocols are recorded.

M. F., History No. 250693, a white married woman, aged 27 years, was admitted to the hospital Nov. 26, 1939. Clinical diagnosis was diffuse hyperplastic goiter. The cardiac mechanism was normal. At the time of the first measurements, Nov. 27, 1939, "before iodine," the basal metabolic rate was +83 per cent. The administration of Lugol's solution (0.5 Gm., three times daily) was started Nov. 29, 1939. Studies were made "during iodine" on Dec. 14, 1939, when the basal metabolic rate was +45 per cent. Following subtotal thyroidectomy, Dec. 16, 1939, 3 c.c. of Lugol's solution were given by rectum, followed by 0.6 c.c. three times daily by mouth, until Dec. 23, 1939. The basal metabolic rate was +17 per cent when observations were made after operation, Dec. 22, 1939. She was discharged Dec. 24, 1939. The surgical pathologic diagnosis was diffuse hyperplastic goiter, with good involution.

S. K., History No. 229168, a white married woman, aged 41 years, was admitted to the hospital Oct. 17, 1939. Clinical diagnosis was mild, toxic, nodular goiter. The cardiac mechanism was normal. Studies "before iodine" were made Oct. 23, 1939, when the basal metabolic rate was +21 per cent. The administration of syrup of hydriodic acid (0.2 c.c., three times daily) was started Nov. 2, 1939. Measurements were made Nov. 13, 1939, "during iodine" therapy, when the basal metabolic rate was +12 per cent. Following operation, Nov. 18, 1939, she was given 0.3 c.c. of Lugol's solution three times daily until Dec. 1, 1939. When studies were made Dec. 1, 1939, the basal metabolic rate was +3 per cent. She was discharged Dec. 2, 1939. Surgical pathologic diagnosis was adenomatous goiter.

L. G., History No. 252938, a white married woman, aged 40, was admitted to the hospital Dec. 7, 1939. Clinical diagnosis was toxic nodular goiter. Normal sinus mechanism prevailed. Observations were made "before iodine," Dec. 9, 1939, when the basal metabolic rate was +30 per cent. The administration of

Lugol's solution (1.3 c.c. three times daily) was started Dec. 9, 1939. Studies were repeated "during iodine" on Dec. 18, 1939, when the basal metabolic rate was -5 per cent. Subtotal thyroidectomy was performed Dec. 20, 1939, and Lugol's solution was given in doses of 1.3 c.c. three times daily after operation. On Dec. 27, 1939, when measurements were again made, the basal metabolic rate was -1 per cent. Lugol's solution was discontinued, and the patient was discharged the same day. Surgical pathologic diagnosis was fetal adenoma of the thyroid gland.

M. H., History No. 252469, a white unmarried woman, aged 49 years, was admitted to the hospital Dec. 3, 1939. Clinical diagnosis was Graves' disease. The cardiac mechanism was normal. Observations were made "before iodine" on Dec. 12, 1939, when the basal metabolic rate was +47 per cent. The administration of Lugol's solution (0.3 c.c. three times daily) was started Dec. 7, 1939. This was discontinued, and the administration of syrup of hydriodic acid (3 c.c. three times daily) was begun Dec. 15, 1939. On Dec. 30, 1939, measurements were repeated when the basal metabolic rate was +24 per cent. Subtotal thyroidectomy was performed Jan. 6, 1940. Lugol's solution (0.6 c.c. three times daily) was given postoperatively until Jan. 12, 1940. Studies of the peripheral blood flow were made Jan. 12, 1940, when the basal metabolic rate was -1 per cent. She was discharged Jan. 15, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

M. P., History No. 246435, a white married woman, aged 54 years, was admitted to the hospital Oct. 5, 1939. Clinical diagnosis was toxic nodular goiter. The cardiac mechanism was normal. On Oct. 24, 1939, "before iodine," when the basal metabolic rate was +34 per cent, studies of the circulation were made. The administration of syrup of hydriodic acid (4 c.c. three times daily) was started Oct. 9, 1939. Studies were made on Nov. 8, 1939, "during iodine," when the basal metabolic rate was +24 per cent. Subtotal thyroidectomy was performed Nov. 14, 1939, and the administration of Lugol's solution (1.3 c.c. twice daily) was started. Studies were repeated Nov. 25, 1939, after operation, when the basal metabolic rate had decreased to +17 per cent. Lugol's solution was discontinued Nov. 28, 1939, and the patient was discharged the following day. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

N. L., History No. 213513, a white single woman, aged 18 years, was admitted to the hospital Feb. 10, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac mechanism was normal. "Before iodine" studies were carried out Feb. 23, 1940, when the basal metabolic rate was -25 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was begun Feb. 22, 1940. Observations were again made during the administration of iodine on March 11, 1940, when the basal metabolic rate was +7 per cent. Lugol's solution (0.6 c.c. three times daily) was substituted for syrup of hydriodic acid on March 12, 1940. Subtotal thyroidectomy was performed March 15, 1940. The administration of Lugol's solution (0.6 c.c. three times daily) was resumed on the first postoperative day and was discontinued March 23, 1940. Studies were made March 23, 1940, when the basal metabolic rate was -2 per cent. She was discharged March 25, 1940. Surgical pathologic diagnosis was diffuse toxic goiter.

C. DiP., History No. 135186, a white single woman, aged 23 years, was admitted to the hospital Feb. 15, 1940. Clinical diagnosis was Graves' disease. The cardiac mechanism was normal. Studies were made on Feb. 28, 1940, "before iodine," when the basal metabolic rate was +53 per cent. The administration of syrup of hydriodic acid (2 c.c. twice daily) was started Feb. 23, 1940, but was replaced by Lugol's solution (0.6 c.c. three times daily) on March 5, 1940. Studies were

made "during iodine" on March 9, 1940, when the basal metabolic rate was +48 per cent. On March 11, 1940, subtotal thyroidectomy was performed and the administration of Lugol's solution (0.6 c.c. three times daily) was resumed; it was discontinued March 15, 1940. Studies "after operation" were made March 18, 1940, when the basal metabolic rate was +17 per cent. She was discharged March 19, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

P. L., History No. 77117, a white married woman, aged 25 years, was admitted to the hospital May 6, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies "before iodine" were made on May 8, 1940, when the basal metabolic rate was +67 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started May 7, 1940. "During iodine," measurements were made on May 23, 1940, when the basal metabolic rate was +38 per cent. Subtotal thyroidectomy was performed May 25, 1940. A single 4-c.c. dose of Lugol's solution in tap water was given per rectum immediately after operation, and the oral administration of Lugol's solution (0.6 c.c. three times daily) was started on the same day and discontinued May 30, 1940. Postoperative measurements were made June 1, 1940, when the basal metabolic rate was +19 per cent. Lugol's solution was discontinued on this day. She was discharged June 2, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

A. P., History No. 258071, a white married woman, aged 39 years, was admitted to the hospital March 26, 1940. Clinical diagnosis was mild, diffuse, toxic goiter. The cardiac rhythm was normal. Measurements were made "before iodine" on March 20, 1940, when the basal metabolic rate was +21 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started March 31, 1940. Studies were carried out "during iodine" on April 9, 1940, when the basal metabolic rate was still +22 per cent. Subtotal thyroidectomy was performed April 12, 1940, after which Lugol's solution (1 c.c. in 1,500 c.c. of saline) was given as an infusion. The oral administration of Lugol's solution (0.6 c.c. three times daily) was started and continued until the day of discharge. "After operation," studies were made on April 20, 1940, when the basal metabolic rate was +6 per cent. She was discharged on April 22, 1940. Surgical pathologic diagnosis was well-involuted hyperplastic goiter.

R. S., History No. 254446, a white single woman, aged 30 years, was admitted to the hospital Jan. 8, 1940. Clinical diagnosis was recurrent Graves' disease. The cardiac rhythm was normal. The first studies were made Jan. 27, 1940, when the basal metabolic rate was +42 per cent. The administration of syrup of hydriodic acid (2 c.c. three times daily) was started Jan. 27, 1940, and replaced by Lugol's solution (1.3 c.c. three times daily) on Feb. 6, 1940. "During iodine," on Feb. 8, 1940, when the basal metabolic rate was +23 per cent, observations were repeated. Subtotal thyroidectomy was done Feb. 17, 1940. The use of Lugol's solution (1.3 c.c. three times daily) was continued. Studies "after operation" were made Feb. 26, 1940, when the basal metabolic rate was +5 per cent. Lugol's solution was discontinued Feb. 27, 1940. She was discharged Feb. 28, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

M. A., History No. 21804, a white single man, aged 56 years, was admitted to the hospital Nov. 15, 1939. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies were made "before iodine" on Nov. 17, 1939, when the basal metabolic rate was +34 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was started after completing the observations. "During iodine," studies were carried out Nov. 24, 1939, when the basal metabolic rate was +9 per cent. Subtotal thyroidectomy was performed

Dec. 1, 1939. Lugol's solution (0.6 c.c. three times daily) was given until Dec. 5, 1939. Postoperative measurements were made on Dec. 7, 1939, when the basal metabolic rate was -3 per cent. He was discharged Dec. 8, 1939. Surgical pathologic diagnosis was diffuse hyperplastic goiter, with good involution.

M. S., History No. 114675, a white married woman, aged 44 years, was admitted to the hospital Dec. 6, 1939. Clinical diagnosis was toxic nodular goiter. The cardiac mechanism was normal. Studies were made "before iodine" on Dec. 10, 1939, when the basal metabolic rate was +33 per cent. The administration of Lugol's solution (1.3 c.c. three times daily) was started Dec. 9, 1939. Measurements were made "during iodine" on Dec. 26, 1939, when the basal metabolic rate was +11 per cent. On Dec. 28, 1939, subtotal thyroidectomy was performed. The use of Lugol's solution (1.3 c.c. three times daily) was continued until Jan. 6, 1940. Studies were made "after operation" on Jan. 5, 1940, when the basal metabolic rate was +8 per cent. Lugol's solution was discontinued Jan. 5, 1940. The patient was discharged Jan. 6, 1940. Surgical pathologic diagnosis was edematous goiter with fetal embryonal adenoma.

H. M., History No. 247647, a white married woman, aged 30 years, was admitted to the hospital Oct. 30, 1939. Clinical diagnosis was diffuse toxic thyroid. The cardiac rhythm was normal. Measurements were made "before iodine" on Oct. 31, 1939, when the basal metabolic rate was +47 per cent. The administration of Lugol's solution (0.6 c.c. three times daily) was begun Nov. 2, 1939. "During iodine," studies were made Nov. 11, 1939, when the basal metabolic rate was +26 per cent. Subtotal thyroidectomy was performed Nov. 15, 1939, and followed immediately by a single 3-c.c. dose of Lugol's solution, in tap water, by rectum, and 0.6 c.c. three times daily by mouth until Nov. 21, 1939. Measurements were made "after operation" on Nov. 22, 1939, when the basal metabolic rate had fallen to +11 per cent. She was discharged Nov. 22, 1939. Surgical pathologic diagnosis was diffuse toxic goiter showing poor involution.

K. H., History No. 89716, a white widow, aged 41 years, was admitted to the hospital Feb. 6, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. Studies were made "before iodine" Feb. 10, 1940, when the basal metabolic rate was +32 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was started Feb. 11, 1940, but was replaced by Lugol's solution (1.3 c.c. three times daily) Feb. 22, 1940. "During iodine," when the basal metabolic rate was +21 per cent, on Feb. 19, 1940, observations were repeated. Subtotal thyroidectomy was performed Feb. 27, 1940. Lugol's solution (3 c.c., in tap water) was given by rectum immediately after operation, and 4 c.c. in tap water by rectum on the following day. The oral administration of Lugol's solution (1.3 c.c. every four hours) was started Feb. 28, 1940. It was not discontinued until discharge. Postoperative studies were made March 6, 1940, when the basal metabolic rate was +9 per cent. She was discharged March 7, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

E. B., History No. 263666, a white widow, aged 40 years, was admitted to the hospital April 10, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. When studies were first carried out, on April 12, 1940, "before iodine," the basal metabolic rate was +52 per cent. The administration of syrup of hydriodic acid (4 c.c. four times daily) was started April 15, 1940. Lugol's solution (0.6 c.c. three times daily) replaced this on May 6, 1940. At the time measurements were made "during iodine," on May 4, 1940, the basal metabolic rate was +23 per cent. On May 9, 1940, subtotal thyroidectomy was performed; Lugol's solution (0.6 c.c. three times daily) was continued until May 15, 1940. "After operation," measurements were made May 15, 1940, when the

basal metabolic rate was +13 per cent. She was discharged May 16, 1940. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

E. S., History No. 100740, a white married woman, aged 52 years, was admitted to the hospital Jan. 27, 1940. Clinical diagnosis was diffuse toxic goiter. The cardiac rhythm was normal. The basal metabolic rate, "before iodine," was +58 per cent on Jan. 29, 1940, when observations were made. The administration of Lugol's solution (0.6 c.c. three times daily) was begun Jan. 29, 1940. Measurements were repeated "during iodine" on Feb. 21, 1940, when the basal metabolic rate was +40 per cent. The first stage of a two-stage subtotal thyroidectomy was performed on the right lobe Feb. 27, 1940. The administration of Lugol's solution (0.6 c.c. three times daily) was continued. On the first postoperative day, Feb. 28, 1940, auricular fibrillation occurred. She was digitalized; the rhythm had reverted to normal the next day. Studies of the circulation were carried out March 9, 1940, when the basal metabolic rate was +14 per cent. Removal of the left lobe of the thyroid was carried out March 11, 1940. Lugol's solution (0.6 c.c. three times daily) and digitalis were continued. Studies were made again March 18, 1940, when the basal metabolic rate was +17 per cent. Digitalis was discontinued March 15, 1940, and the auricular fibrillation did not recur. Lugol's solution was discontinued March 17, 1940. She was discharged March 19, 1940. Surgical pathological diagnosis was: right lobe, diffuse hyperplastic goiter; left lobe, diffuse hyperplastic goiter, with chronic strumitis.

A. S.,I History No. 230995, a white married woman, aged 41 years, was admitted to the hospital Feb. 27, 1940. Clinical diagnosis was toxic nodular goiter. The cardiac rhythm was normal. In this case the cardiac output was measured, in addition to the other circulatory measurements. "Before iodine," on Feb. 28, 1940, the peripheral blood flow was measured when the basal metabolic rate was +60 per cent. On the following day, when the basal metabolic rate was +54 per cent, the cardiac output was measured. The administration of Lugol's solution (0.6 c.c. three times daily) was started Feb. 29, 1940. "During iodine," measurements of peripheral blood flow were made March 7, 1940, when the basal metabolic rate was +18 per cent. On the next day, when the basal metabolic rate was +15 per cent, the cardiac output was estimated. Subtotal thyroidectomy was carried out March 9, 1940. Lugol's solution (3 c.c., in tap water) was given by rectum immediately after operation, and the oral administration of 0.4 c.c. three times daily was started. On March 10, 1940, Lugol's solution (4 c.c., in tap water) was given by rectum, in addition to that by mouth. Measurements "after operation" were made on March 16, 1940, when the basal metabolic rate was +4 per cent. On the following day, when the basal metabolic rate was −5 per cent, the cardiac output was again measured. Lugol's solution was discontinued March 19, 1940, and she was discharged the next day. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

A. S.,II History No. 260735, a white married woman, aged 42 years, was admitted to the hospital March 11, 1940. Clinical diagnosis was Graves' disease. Auricular fibrillation was present. Studies were made "before iodine" on March 16, 1940, when the basal metabolic rate was +52 per cent. After completion of these observations she was given 1.4 Gm. of digitalis on March 16, 0.4 Gm. on March 17, 0.3 Gm. on March 18, and 0.1 Gm. twice daily from March 19, 1940, until operation. A second set of studies "before iodine" was made on March 23, 1940, in order to evaluate the effect of digitalis. The basal metabolic rate, at this time, was +64 per cent. The administration of syrup of hydriodic acid (4 c.c. four times a day) was started March 23, 1940. It was replaced by Lugol's solution (0.6 c.c. three times daily) on April 26, 1940. The basal metabolic rate

was +24 per cent on April 27, 1940, when the peripheral blood flow was measured; at this time the patient was under the influence of digitalis and iodine. Subtotal thyroidectomy was performed May 4, 1940, and Lugol's solution (0.6 c.c. three times daily) was continued. The administration of digitalis (0.1 Gm. twice a day), which had been discontinued after operation, was begun again on May 9, 1940, and continued thereafter. Postoperative measurements were made on May 9, 1940, when the basal metabolic rate was +13 per cent. Lugol's solution was discontinued May 10, 1940. She was discharged May 11, 1940; the auricular fibrillation was still present. Surgical pathologic diagnosis was diffuse hyperplastic goiter.

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DISCUSSION

DR. EUGENE F. DUBOIS, NEW YORK.—Dr. Stewart and Dr. Evans, under the conditions of their experiments in these studies, have shown that there is a very beautiful parallelism between the basal metabolic rate, peripheral blood flow, and skin temperature. I think it is exceedingly important, however, not to jump to the conclusion that skin temperature is necessarily a good index of peripheral blood flow. It is a good index if the normal relationship is maintained between heat loss by radiation, convection, and vaporization, but, if any of these factors is changed, there may be big discrepancies between surface temperature and peripheral blood flow and heat loss.

We have studied a good many conditions with the respiration calorimeter, and have found that anything that increases vaporization or convection will cause a drop in skin temperature at the time when heat loss and peripheral blood flow are increased.

For example, after exercise the skin temperature goes down markedly because the increased vaporization is cooling the skin at a time when heat loss is increased.

The formula that has been presented seems complicated, but it apparently works out well in the studies that we have made of the direct heat loss in the calorimeter.

I want to emphasize the fact that the authors have studied heat loss, not heat production. There may be big differences when the body temperature is changing. I also want to emphasize the fact that they have studied the surface temperature and the peripheral blood flow of the whole skin, and not simply the hands and feet. The hands and feet represent about 12 per cent of the total surface, and a great many people have neglected the other 88 per cent.

This rather complicated method has been checked in a good many laboratories, and I think is generally accepted. It certainly gives great promise of affording useful information in many conditions other than Graves' disease.

DR. J. MURRAY STEELE, NEW YORK.—I should like to ask just two questions. One is, What is the normal value of peripheral blood flow per square centimeter with this method? Why did you discard what I took to be a fall in rectal temperature in both cases? With the known constancy of rectal temperature, a change of a few tenths of a degree may often be more important than one of many degrees in the surface temperature.

DR. DAVID I. ABRAMSON, CINCINNATI.—In support of this work, I should like to say that we have used the venous occlusion plethysmographic method in studying the forearm, which we consider a very constant bed, and have found that if a hyperthyroid patient has a basal metabolism of +60 per cent, or so, the blood flow in the forearm will be as high as 6 c.c. per minute per 100 c.c. of limb volume, whereas in a normal person it is about 1 to 2 c.c. Following thyroidectomy, the blood flow returns, within a few days, to the normal level. We have observed this in a number of hyperthyroid cases.

DR. STEWART.—I would like to emphasize one or two points. These measurements afford objective evidence which confirms the clinical impression that the flushed appearance and warm skin of patients with Graves' disease indicate an increase in peripheral blood flow.

The partition of the cardiac output among the various parts of the human body is not known. Blalock has approximated this for certain of the arteries in dogs, but how much of the total output per minute is allocated to the different organs of the human body is not known.

In the first case that Dr. Evans demonstrated, we made measurements of cardiac output at the time that the peripheral blood flow was measured. This patient's total cardiac output was 6 L. per minute, which is a tremendous increase. In terms of liters per square meter, to which the measurements of peripheral blood flow were reduced, the cardiac output amounted, before treatment, to 3.48 L. per square meter per minute (the normal is about 2). At that time, the peripheral blood flow in that patient amounted to 212 c.c. per square meter per minute when the basal metabolic rate was +60 per cent.

After iodine therapy, this value fell to 2.53 L. per square meter per minute, when the blood flow was 125 c.c. and the basal metabolic rate +18 per cent. Then, after operation, the cardiac output fell to 2.02 L. per square meter per minute, which is normal, and the blood flow was 69 c.c. and the basal metabolic rate +6 per cent. Thus, the total cardiac output and the output per unit of body surface area were adequate to divert these added amounts of blood to the skin.

Finally, the further decline in all of the functions which we measured after thyroidectomy demonstrates that operation accomplishes something for cardiovascular system that is not achieved by the use of iodine.

DR. EVANS.—Referring to Dr. Steele's question about the normal values. Hardy and Soderstrom have found that about 0.015 c.c. per square centimeter per minute is the normal volume of blood flow. We have calculated ours in square meters, which would be approximately 15 c.c. per square meter. It must be remembered that that is at the upper limit of our room temperature, and probably decreases to just a few cubic centimeters at a lower room temperature, down to the lower level of the cool zone.

Of several patients with myxedema whom we have studied, whose peripheral blood flow was reduced, one, in particular, had a peripheral blood flow of 8 c.c. at the upper level of room temperature.

In reference to the rectal temperature, it is quite true that, because of the weighting of 80 per cent for the deeper tissues, small variations in rectal temperature may make quite a marked change in the calculated peripheral blood flow. We have found that, in most instances, this is beautifully counterbalanced by the changes in skin temperature; most of them are remarkably constant, with the exception of the first two phases. There is a good deal of vasomotor instability, as you probably observed. In the later phase, after operation, when the vasomotor system seems to cool off, so to speak, these changes compensate one another.

CIRCULATORY REACTIONS IN THE GASTROINTESTINAL TRACT ELICITED BY LOCALIZED CUTANEOUS STIMULATION

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ST. LOUIS, MO.

LOCALIZED cutaneous stimulation by means of thermal, mechanical, and chemical agents has long been utilized in the treatment of visceral and other deeply located lesions, but there has been no general agreement regarding the mechanisms through which its beneficial effects are brought about. The assumption that alleviation of pain, by applying heat or other stimulating agents to the skin, is associated with circulatory changes in the diseased area is supported by clinical and experimental data. Certain experimental data also support the assumption that the reflex responses of the musculature of visceral organs which are elicited by localized cutaneous stimulation are accompanied by reflex changes in the tonus and caliber of the blood vessels in question.

Reflex responses of the gastric musculature, including the pyloric sphincter, elicited by warm and cold applications to the skin of the epigastric area have been described in detail by Freude and Ruhmann[1] (1926); their observations were made with the fluoroscope. Comparable reactions of the gastric musculature, according to Ruhmann[2] (1927), may be elicited by appropriate, localized mechanical or chemical stimulation of the skin. Ruhmann also pointed out that the response of the gastric musculature occurs only after a change in the tonic state of the cutaneous blood vessels in the area stimulated has taken place, and that the blood vessels of the stomach undergo a change in tonus corresponding to that of the cutaneous vessels in the area stimulated. These statements are in full accord with certain clinical observations reported by Boas[3] (1926). He noted that warm applications in the epigastric area may cause a peptic ulcer, the existence of which had not been suspected, to bleed. The cessation of bleeding, in cases of bleeding peptic ulcer, effected by cold applications to the epigastrium is undoubtedly the result of vasoconstriction in and about the area of ulceration.

Circulatory responses in other viscera, elicited by localized cutaneous stimulation in appropriate areas, also have been recorded. Freude and Ruhmann[1] produced marked hyperemia of the ascending colon by applying heat to the skin in the lower abdominal area while the colon was exposed during an abdominal operation. Ruhmann[4] (1933) reported that warming the skin of an upper extremity caused a marked increase in the volume of blood circulating in the thoracic viscera. Keep-

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ing the left arm and hand in warm water until the skin became hyperemic resulted, in certain cases, in the relief of coronary vasospasm.

Although localized cutaneous stimulation by means of various agents is widely employed in the treatment of disease, there is no general agreement regarding its therapeutic value, or the manner in which deep lesions, particularly lesions of visceral organs, are influenced by it in cases in which it is beneficial. It has been assumed, without adequate supporting data, that thermal stimulation of the skin by means of warm and cold applications exerts direct thermal effects on the underlying viscera. Even if a direct thermal effect could be demonstrated in cases in which the viscus in question is separated from the area of stimulation only by the thin abdominal wall, it could not be assumed that the stimulus has the same effect when it is applied to the skin of the back or that of an extremity. The assumption that the circulatory changes which are elicited in visceral organs by cutaneous stimulation are reflex phenomena mediated through segmental and intersegmental reflex arcs seems more plausible, and is supported by certain clinical and experimental data.

The present investigation was undertaken to determine more accurately than is indicated by the data hitherto available whether appreciable circulatory changes in visceral organs can be brought about by means of localized cutaneous stimulation, and whether the changes which occur are direct effects of the stimulation employed, or are reflex phenomena.

METHODS

The experiments were carried out on decerebrated cats. Decerebrate preparations were used in order to avoid the vitiating effects of anesthesia. Decerebration was performed with the animal under ether anesthesia, but the stimulation experiments were not begun until the anesthetic effect of the ether and the shock of the operation had subsided.

Warm and cold applications and vacuum cups were employed as stimulating agents; they were applied to the skin of the back and lateral surfaces of the trunk, from which the hair had been removed. The changes brought about in the blood vessels of the stomach and intestine were observed with the viscus exposed through a midventral incision, and were recorded photographically and plethysmographically. In order to ascertain whether the visceral blood vessels could react to cutaneous stimulation in the absence of segmental cutaneovisceral reflex arcs, some of the animals used were subjected to bilateral section of the splanchnic nerves and extirpation of the sympathetic trunks in the lumbar segments before the stimulation experiments were carried out.

EXPERIMENTAL DATA

In all of the decerebrate animals, except those which had been subjected to bilateral section of the splanchnic nerves and extirpation of the lumbar segments of the sympathetic trunks, thermal stimulation and cupping of the skin of the back and lateral body surfaces elicited changes in the blood vessels of the stomach and intestine which were of the same order as those of the cutaneous vessels in the area stimulated. The application of cold packs to the skin of the back or lateral

body surface, from the fifth or sixth thoracic segment caudad, consistently resulted in vasoconstriction in the stomach and intestine. The application of warm packs to the same areas, raising the skin temperature to 45° to 50° C., consistently caused vasodilation in the stomach and intestine. The optimum temperature of warm applications for the production of vasodilatation in the gastrointestinal tract in the cat seems to lie within this range. When packs were applied which were warm enough to raise the local skin temperature to 52° C. or higher, the initial vascular response in the gastrointestinal tract was not vasodilation, but vasoconstriction. Cutaneous stimulation by means of the vacuum cups resulted in vasodilatation in the corresponding portion of the gastrointestinal tract of approximately the same degree as that caused by moderate warming of the skin in the same area.

The changes in the caliber of gastric and intestinal blood vessels brought about by the varieties of cutaneous stimulation which we employed in these experiments became apparent within a few seconds after the application of the stimulus, and reached their maximum within a relatively short interval. This is illustrated most satisfactorily by the plethysmograms which were obtained from loops of the small intestine (Fig. 1). The rise in the tracing caused by local warming of the skin and the fall caused by local cooling of the skin may take place relatively abruptly, as illustrated in the upper part, or more gradually, as illustrated in the lower part of Fig. 1.

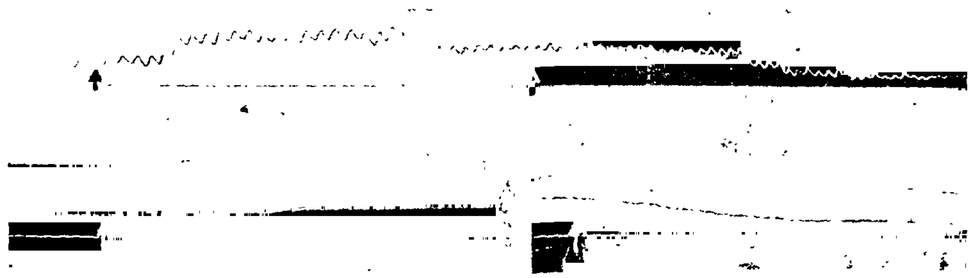
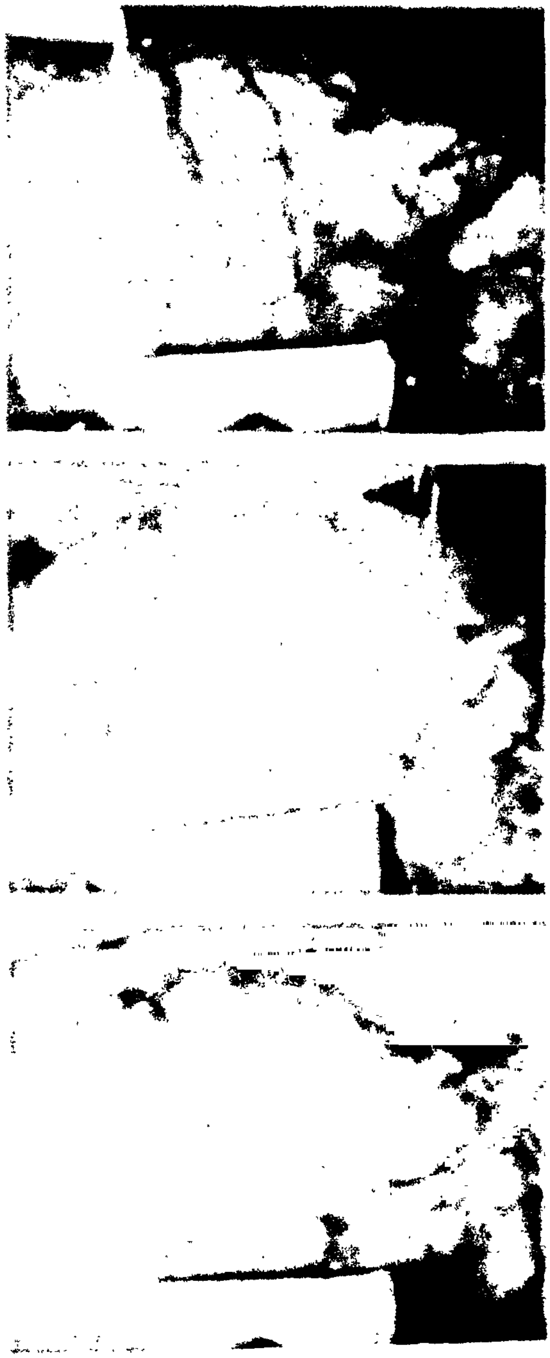


Fig. 1.—Plethysmograms of a loop of the small intestine of the decerebrate cat during localized cutaneous stimulation by means of warm and cold applications. Initiation of stimulation is indicated by arrows. *A*, Response to warm applications; *B*, response to cold applications.

Photographs of segments of the gastrointestinal tract which were obtained during intervals of vasodilatation caused by local warming of the skin and during intervals of vasoconstriction caused by local cooling of the skin, when compared with those which were made when the skin was not being specifically stimulated, indicate that the changes in caliber brought about by this kind of stimulation are more marked in the smaller blood vessels than in the larger ones. Direct observation, with low magnification, also supports this conclusion. When the skin was warmed, the smallest vessels in the affected segments of the gastrointestinal tract which could be seen before the thermal stimulus was applied became more apparent, and many of them could be traced farther than before. Also, many small vessels which could not be seen



ences in the caliber of the larger vessels. The caliber changes in the smaller vessels, as shown by a comparison with the photographs which were made when no specific cutaneous stimulation was being applied, are sufficient to warrant the conclusion that the volume of blood circulating through the affected segments of the gastrointestinal tract is markedly increased by local warming and markedly decreased by local cooling of the skin.

The circulatory changes in the gastrointestinal tract which were observed and recorded in our experiments obviously cannot be explained on the assumption that the gastrointestinal blood vessels were influenced directly by the stimulus employed, for the stimulating agent was applied to the skin of the back and lateral surface of the trunk, while the viscus under observation was exposed through a mid-ventral incision in the abdominal wall. The assumption that these circulatory changes were brought about reflexly through segmental and intersegmental reflex arcs which include sympathetic neurons (Fig. 3) is supported by the fact that they failed to appear in decerebrated animals in which the splanchnic nerves had been severed and the lumbar segments of the sympathetic trunks removed. Ruhmann[2] also reported failure to produce circulatory changes in visceral organs by means of localized cutaneous stimulation in human subjects after blocking the sympathetic ganglia through which the viscera in question are innervated.

Reflex vasoconstriction in the gastrointestinal tract, mediated through segmental and intersegmental cutaneovisceral reflex arcs, can be explained satisfactorily, for the sympathetic nerves of the abdominal viscera, components of which constitute the distal units in the efferent limbs of the cutaneovisceral reflex arcs, include vasoconstrictor fibers. The assumption that these nerves also include vasodilator fibers is supported by conclusive experimental data (Burn,[5] 1938). Consequently, reflex vasodilatation in the gastrointestinal tract, mediated through segmental and intersegmental reflex arcs, can also be explained satisfactorily on the basis of available anatomic and physiologic data.

Because of the arrangement of the visceral components of the spinal nerves, cutaneous stimulation in an area which involves but a few segments of the body may evoke reflex vascular responses in a relatively extensive portion of the gastrointestinal tract. The somatic rami of the spinal nerves are arranged segmentally, although the areas of distribution of adjacent spinal nerves overlap to some extent; but the efferent components of the visceral rami of these nerves effect synaptic connections with sympathetic ganglion cells, the distribution of whose axons is not limited to a single segment and parts of the adjacent ones. The blood vessels in a relatively long segment of the gastrointestinal tract, consequently, may be influenced by impulses conducted through the visceral efferent components of a single spinal nerve.

The observation recorded above, that, as a result of cutaneous stimulation, the smaller vessels in the gastrointestinal tract undergo more

marked changes in caliber than the larger ones, is in full accord with the opinion of Burn,[5] based on his own experience and an exhaustive review of the literature, that the sympathetic vasodilator fibers innervate the peripheral branches of the intestinal arteries. Therefore, dilatation of the terminal arterial branches, including the arterioles and the capillary bed, may facilitate the flow of blood through the organ, while the general blood pressure is safeguarded by the tonicity of the larger arteries.

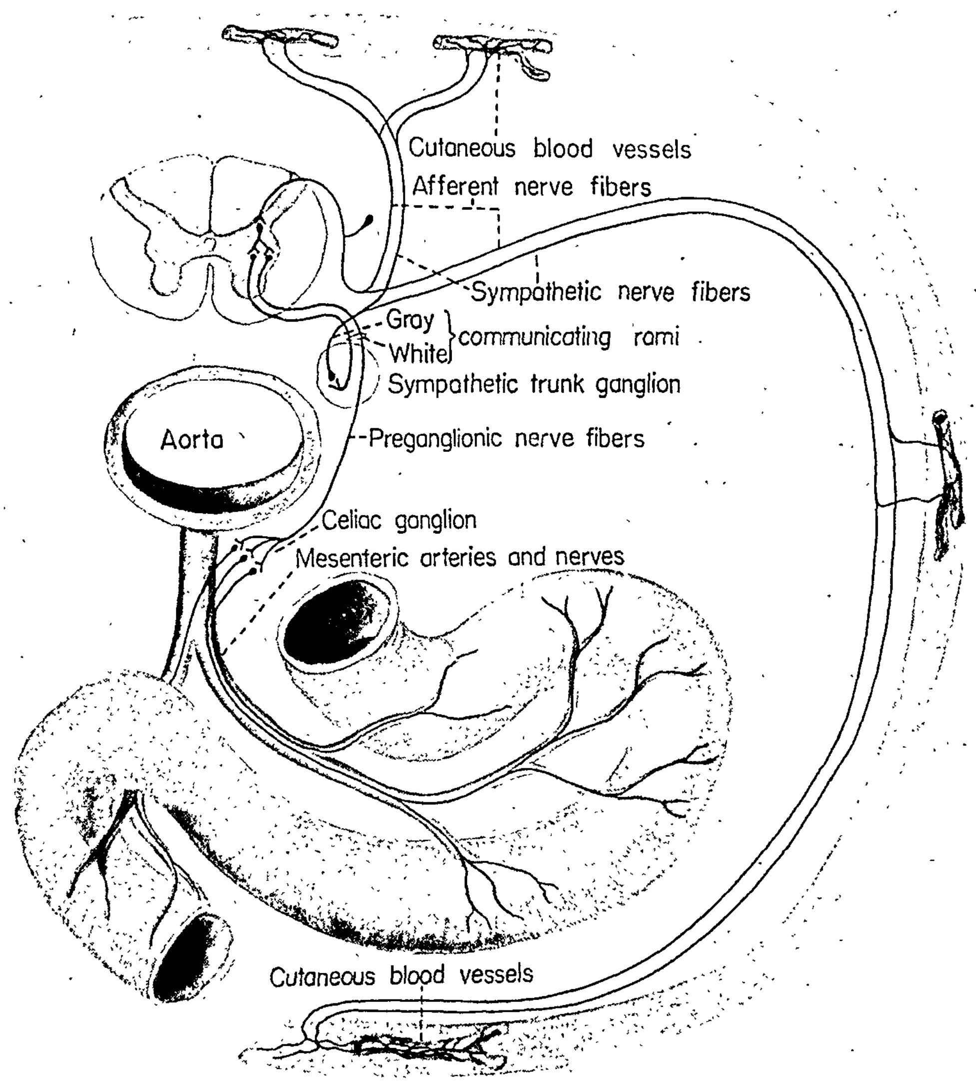


Fig. 3.—Diagrammatic illustration of cutaneovisceral vasomotor reflex arcs.

In all of our experiments in which the application of warm packs or the alternate application of warm and cold packs in the same cutaneous area was prolonged, the skin in this area became markedly hyperemic. The localized cutaneous hyperemia produced in this manner persisted for some time after removal of the stimulating agents. During this interval, cooling of the skin in the hyperemic area did not result in vasoconstriction in the gastrointestinal tract, nor did the further use

of warm applications result in increased vasodilatation in the viscus. This is in full accord with the observation reported by Ruhmann,[4] namely, that the gastrointestinal musculature does not respond reflexly to local warming of the skin until dilatation of the cutaneous blood vessels in the area stimulated has taken place. These observations support the assumption that stimulation of the receptors involved in cutaneovisceral vasomotor reflexes is associated with changes in the tonic state of the cutaneous blood vessels.

SUMMARY AND CONCLUSIONS

In this series of experiments, circulatory changes in the gastrointestinal tract were produced by localized stimulation of the skin. The changes in the caliber of the gastrointestinal vessels which were observed and recorded corresponded to those produced in the cutaneous vessels in the area stimulated. Moderate, localized warming of the skin (to 45° to 50° C.) and the application of vacuum cups produced vasodilatation in the cutaneous area stimulated and in the corresponding segments of the gastrointestinal tract. Localized warming of the skin to 52° C., or more, caused initial vasoconstriction in the gastrointestinal tract. Moderate, localized cooling of the skin resulted in vasoconstriction in the cutaneous area stimulated and in the corresponding segments of the gastrointestinal tract. The caliber changes in the gastrointestinal blood vessels were more marked in the smaller ones than in the larger.

The vasoconstriction and the vasodilatation in the corresponding portions of the gastrointestinal tract which were brought about by the use of cold and warm applications, respectively, were sufficiently marked to warrant the conclusion that the volume of blood flowing through the affected segments of this viscus is markedly decreased by local cooling and markedly increased by local warming of the skin.

The circulatory changes in the viscera which are produced by localized cutaneous stimulation can be explained most satisfactorily as reflex reactions mediated through segmental and intersegmental cutaneovisceral reflex arcs. Stimulation of the receptors involved in these reflex reactions is probably associated with a change in the tonic state of the cutaneous blood vessels in the area in question.

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APPLICATIONS OF PHOTOELECTRIC PLETHYSMOGRAPHY IN PERIPHERAL VASCULAR DISEASE*†‡

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THE great interest in the peripheral circulation in recent years led to the development of many observational methods and their application to the study of physiologic and clinical problems in this field. These methods use changes in skin temperature, in color and volume of the part, in electrical conductivity, in thermal conductivity, in heat radiation and heat loss, in insensible perspiration, and in arteriovenous oxygen differences as criteria of the blood flow and the state of the blood vessels in the observed part. No one of these methods permits a direct record of blood flow, although the results obtained by all of them agree, under circumstances suitable for their individual application, as to the qualitative character of the changes in blood flow. The addition of other observational techniques renders a service if they possess any advantages in application over previous methods.

The photoelectric plethysmograph has been intensively studied and extensively applied in this laboratory.[1-5] Our experiences in using this method on patients have proved profitable in its refinement and evaluation as a clinically useful tool. Some of these data are detailed here in order to direct attention to the advantages of the method.

METHOD

The essentials of, and the sources of error in, photoelectric plethysmography have been described in other communications.[1-5] Certain refinements and conveniences in the construction and application of the plethysmograph, and in recording, may be added here. Fig. 1 shows the present form of the plethysmograph for exploring the vasculature of various skin areas. When prolonged, continuous observations are desired on the fingers or toes, it is convenient and preferable to attach a thin copper shelf for the digit to rest on. Wrapping the copper sheet about the digit helps greatly to secure proper immobilization, but one must avoid any pressure on the digit. It is still better to prepare an *incomplete* plaster of Paris cast of the digit when it is in position in the copper trough of the plethysmograph. This secures complete immobilization without any interference with the blood supply, but one must wait for the cast to dry before using it, for temporary local vascular disturbances result from the temperature changes induced by the drying of the cast.

The best way to apply the plethysmograph to the skin of the head, to the ear, or to the nasal septum is to suspend it from a plaster of Paris cast of the cranium which rests on the head of the subject (Fig. 2). This cast is prepared in advance by covering the hair with a bathing cap (which is later removed), and then apply-

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†These and similar data were exhibited at the 18th annual session of the American Congress of Physical Therapy, September 5 to 8, 1939, New York City.

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ing plaster of Paris bandages until a sufficiently rugged cast results. As the bandage strip is wrapped on, a small brass plate, carrying a screw, is set in the bandage. The screw later receives a ball for a ball-and-socket joint, which affords a convenient means of adjusting the plethysmograph to varying skin contours. This arrangement has very important advantages from the viewpoint of rigidity of support of the plethysmograph and the comfort of the subject. The cast, since it is individually fitted, uniformly distributes the weight over the entire head, and so avoids local pressure, which may become extremely distressing. Subjects have carried several plethysmographs on such a cast for several hours without discomfort and have even fallen asleep during observations.

Fig. 1.—The photoelectric plethysmograph. *P. C.*, Photoelectric cell in housing. *L.*, Pencil flashlight bulb, mounted on carrier. The bulb is actually inside the brass tube, about 5 mm. from the skin surface. *F.*, Filter carrier, with small round disc of glass serving as filter.

Recording may be done with high frequency instruments, such as the string galvanometer, but their only advantage is for wave form analysis. They are not necessary for routine plethysmography, for which we use modified milliammeters. The pointer of the meter is bent so that its end rotates in the axis of rotation of the coil. A small mirror mounted on the end of the pointer provides for photographic recording. (We owe this suggestion to Doctor Con Fenning, of the University of Utah.) The records so obtained are quite suitable for estimating the arterial supply, using the "filter" technique.[1] Comparison of the amplitude of the oscillations so recorded and also simultaneously recorded with a high frequency instrument shows that little error is introduced by substituting the inexpensive milliammeters, which have the added advantage of being insensitive to alternating current oscillations.

Illumination of the skin area is provided by a pencil-type flashlight bulb. This type of bulb, with its "drop" lens, provides a concentrated light sufficiently strong for the purpose. Stronger lights give rise to local heating effects. Even these small bulbs will gradually raise the temperature (as measured by a thermocouple) when the blood supply is normal, but in ischemic skin this effect develops

so slowly that estimations of blood supply which can be made immediately after turning on the light are not affected. The bulbs may be operated either on direct current (dry cells, or preferably, a storage battery) or, when millivoltmeters are used for recording, on alternating current. When the latter is used, a voltage regulator is absolutely essential, for, otherwise, the fluctuations in line voltage caused by varying illumination will produce gross distortions in the record.

The photoelectric cell is most conveniently mounted in a microphone connector, in which the female element is placed in the male socket or cap. Since this cap comes provided with a guide pin, a slot may be cut in the plethysmograph to receive the pin. This provides for swift, accurate, and rigid placement of the photoelectric cell in the plethysmograph, and for convenient removal of the cell when it is necessary to replace it or guard against breakage.

Fig. 4.—The photoelectric plethysmographs mounted in a plaster of Paris cast for simultaneous recording of vascular reactions in skin of the forehead and ear.

PHOTOELECTRIC PLETHYSMOGRAPHY IN THE STUDY OF VASCULAR REACTIONS

The value of photoelectric plethysmography as a control in surgery of the sympathetic nervous system is indicated in Fig. 5, in which the pronounced vasoconstrictor reflex in the finger in response to a deep breath is compared with the extremely small effect in the toe of an epileptic subject in whom a lumbar sympathectomy had been done. The completeness of the denervation of the toe is indicated by the almost total absence of vasoconstrictor reactions, whereas in the finger there are a definitely decreased volume and volume pulse. The innervated toe

usually gives as strong a response to this stimulus as the finger. Smithwick[6] has apparently made a similar application of the photoelectric plethysmograph. Since changes in volume may occur independently of variations in arterial tone,[5] the changes in the volume pulse may be recorded as described elsewhere,[5] in order to follow the changes in arterial tone alone.

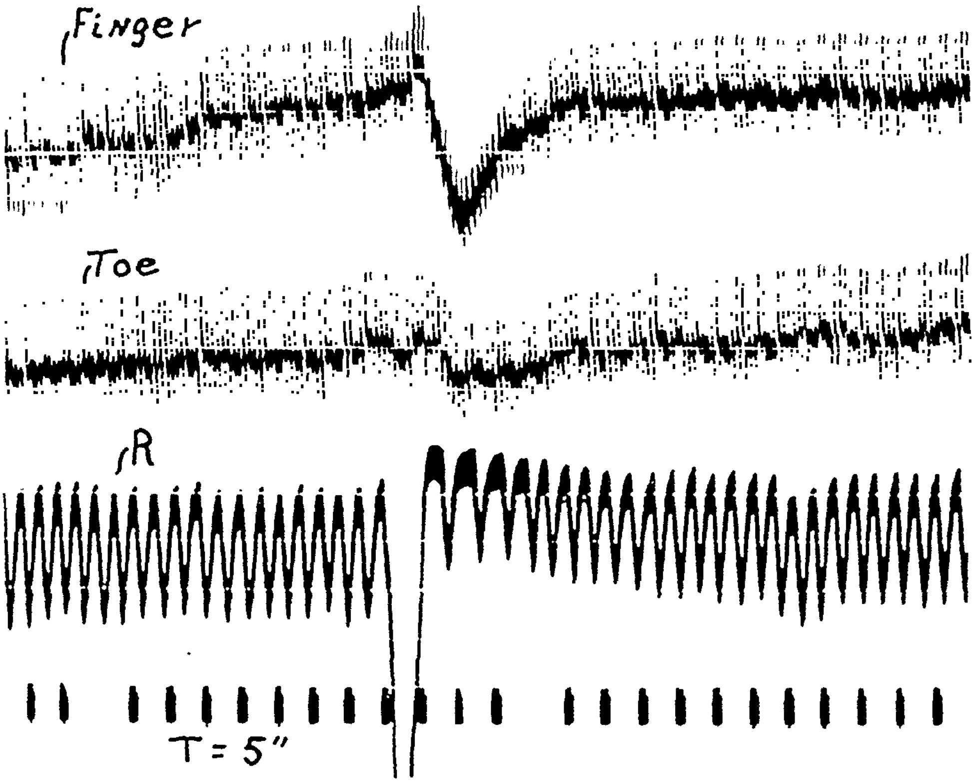

Fig. 3.—Photoelectric plethysmograms of the finger (upper record) and toe (lower plethysmogram) in a case of epilepsy, after lumbar sympathectomy. Deep breath, as indicated on the respiration record. Time: 5 seconds.

The observation of spontaneous activity of the digital arteries by means of the photoelectric plethysmograph (Fig. 4*A*) is particularly interesting in cases of Raynaud's disease (Fig. 4*B*). This patient (a woman, 70 years old, whose blood pressure was 140/95) had Raynaud's syndrome in both hands, the toes, and lips. The figure records activity in the finger pads of the right middle and little fingers. The latter's blood supply, as measured by the "filter" technique (see below), was nearly normal, while the middle finger had a very poor supply. The differences in spontaneous activity of the vessels of the two fingers were quite striking, particularly when compared with the uniformity in spontaneous activity usually exhibited simultaneously by all of the finger arteries in normal subjects (Fig. 4*A*). A similar independence in the activity of the arteries of the middle fingers of the two hands was observed. Both of these fingers had about an equally poor blood supply. Although it is theoretically possible that such independence in activity

depends on innervation, it seems more probable that it resides in peculiarities in the smooth muscle. A suggestion of independence in activity occurs only occasionally in normal subjects. These phenomena are best explained by Lewis' local fault concept.[7]

MEASUREMENT OF THE SKIN BLOOD SUPPLY WITH THE PHOTOELECTRIC PLETHYSMOGRAPH

Securing objective data concerning the blood supply of various skin areas in relation to vascular disorders and the effects of therapy on these disorders is one of the useful applications of this instrument. The principle of the photoelectric method depends on the estimation of the amplitude of the volume pulse in the observed area; this is used as a measure of arterial flow. This relation has been discussed elsewhere.[1] The method has certain advantages over mechanical plethysmographs, namely, speed, extreme sensitivity, convenience, and applicability to areas which cannot be explored by the mechanical plethysmograph.

One proceeds as follows: The plethysmograph is brought into contact with the skin area. The volume pulse is then recorded (Fig. 5). The record is then calibrated in arbitrary units (whose blood equivalent has been discussed elsewhere[1]). The "filter," which is simply a thin sheet of uncolored glass about .042 inch thick (thin microscope slide glass serves), is swung into place between the photocell and the transilluminated skin. This results in the absorption of a constant *fraction* (not a constant amount) of the light reaching the photocell, and so automatically calibrates the intensity of the illumination and the amount of amplification. The deflection in the record so produced is then compared with that of the volume pulse. The amplitude of the volume pulse (measured in mm. at arrow) is then divided by the deflection caused by the "filter" (also measured in mm.). The result is the amplitude of the volume pulse expressed in "filter units." (An error in the measurement of the volume pulse should be pointed out. Either it must be measured always on the same side of the light beam or shadow, or a correction for the width of the beam must be made. This error increases relatively as the volume pulse decreases in recorded amplitude.) When the string galvanometer is used to record the volume pulse on narrow paper, the string is shunted by high resistance during the recording of the volume pulse and by lower resistance during the "filter" deflection. This is necessary in order to secure adequate amplitude of the volume pulse for measurement. The error introduced by the string shunt is ignored, for this is a constant error which does not influence comparisons. The data below and in Fig. 5 were so obtained.

It is necessary to point out that grossly altered dynamics of the heartbeat or of the large arteries will affect the dependability of the volume pulses in skin areas as criteria of the flow through these areas, and of the state of constriction or dilatation of the small arteries and arterioles involved. This source of error is illustrated in cases of patent ductus arteriosis, in which there is a very large pulse pressure. The extraordinarily large volume pulses in these patients' fingers do not appear to represent a correspondingly large blood flow in the fingers, but rather are the result of the large pulse pressure.

The data in Fig. 5 were obtained in a case of Raynaud's disease. The reduction in skin blood supply, as compared with normal values,[1] is evident. These values were obtained one week after right-sided cervical sympathectomy (involving ganglionectomy), when the condition

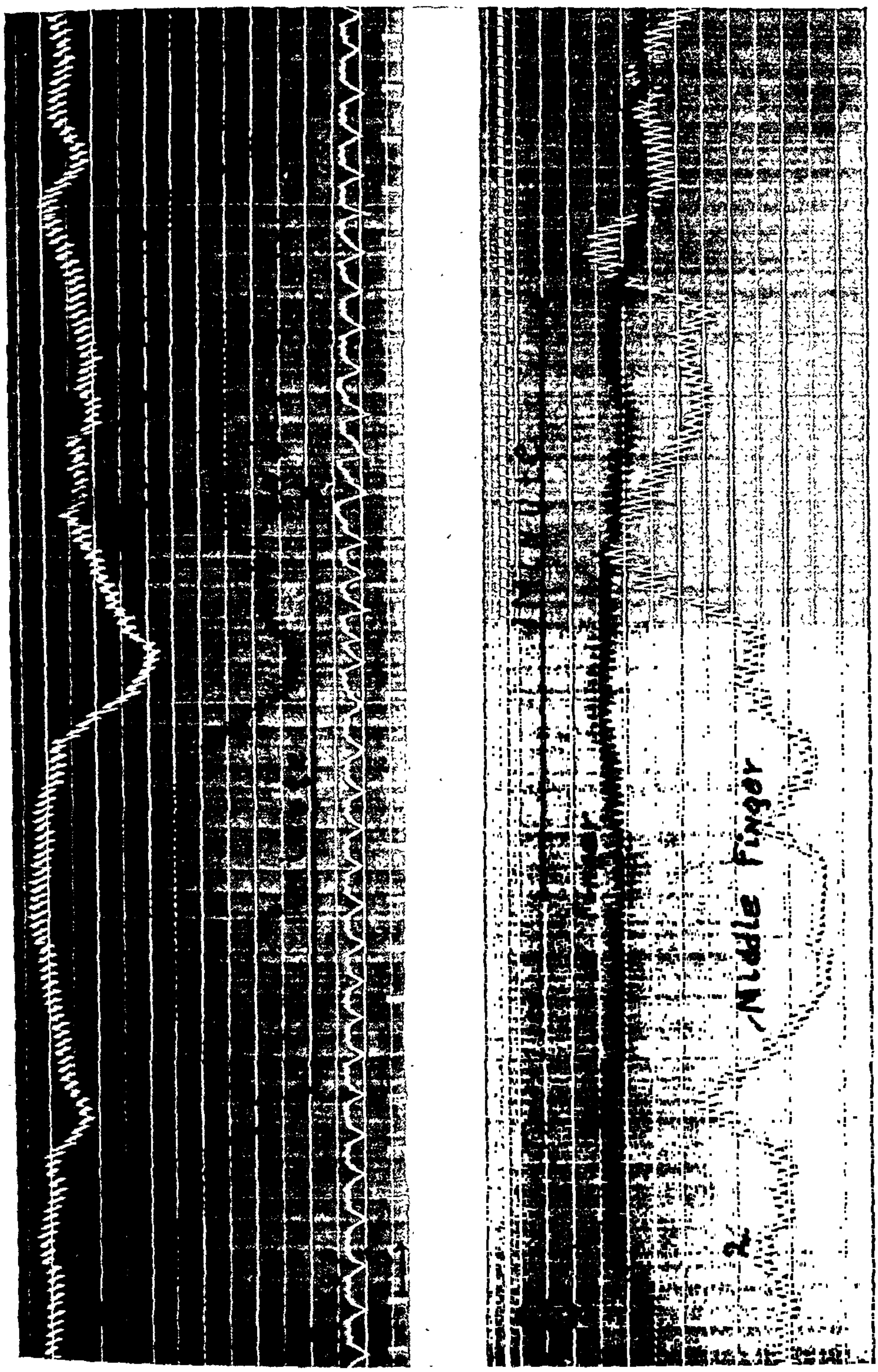

Fig. 4.—Photoelectric plethysmograms of finger pads. *A*, Normal subject; two fingers of same hand; spontaneous waves. *B*, Raynaud's disease; little and middle fingers of right hand; spontaneous waves.

of the patient was poor. The cutaneous ischemia, which was not limited to the right side, was probably the result of a general postoperative impairment of the circulation. This phenomenon is more clearly indicated in Table I. The ability of the plethysmograph to follow the changes

TABLE I

SKIN AREA	11/23/38 78° F.	12/2/38 80° F.	3/4/39 80° F.
Right Hand:			
Index finger	0.58	0.28	0.13
Middle finger	0.73	0.46	0.12
Ring finger	0.67	0.59	0.13
Little finger	0.15	0.0	0.0
Thumb	0.20	0.35	0.23
Left Hand:			
Index finger	0.83	0.12	0.62
Middle finger	1.55	0.28	1.00
Ring finger	0.80	0.21	1.4
Little finger	1.0	0.36	1.7
Thumb	0.73	0.19	1.2
Forehead (right)	0.80	0.31	0.63
Forehead (left)	0.80	0.31	0.80
Nose (right)	0.70	0.45	0.55
Nose (left)	1.00	0.45	1.2

Table I.—Blood supply, as judged by the amplitude of the volume pulses of the pads of the fingers and of the skin of the forehead and nose before and after right-sided cervical sympathectomy. Raynaud's disease. Operation on Nov. 25, 1938. Patient in weakened condition on Dec. 2, 1938. Note the decreased blood supply to all areas on this date. Volume pulses are expressed in "filter" units.

in the skin circulation caused by sympathectomy is well illustrated in this case. Four months after operation, the skin blood supply was reduced on the right side, as compared with the preoperative level. It is interesting to note that this effect likewise occurred on the forehead and nose, although it was less marked here. The instrumental evaluation of the results of interrupting the postganglionic fibers agreed with the clinical impression that the circulation was impaired in the areas affected by the operation. The completeness of the sympathectomy was apparent from the results of applying suitable vasoconstrictor stimuli, such as immersing the opposite hand in ice water (Fig. 6). No reflex constriction occurred in the sympathectomized hand. In contrast, immersion of the right hand in ice water elicited the usual reflex constriction in the opposite hand, whose sympathetic innervation was still intact. In such experiments, arterial constriction is indicated by the decrease in the volume pulse, as well as by the decrease in volume which is caused by the diminished engorgement of all vessels in the pad as a result of decreased flow, which, in turn, is the result of the arterial constriction.[5] No change in volume or volume pulse occurred on the sympathectomized side when vasoconstrictor stimuli were applied. Since the denervated side did not respond, there was no evidence of a secretion of adrenalin in response to the cold stimulus, although current theory postulates an increased sensitivity of sympathectomized extremities to circulating adrenalin.

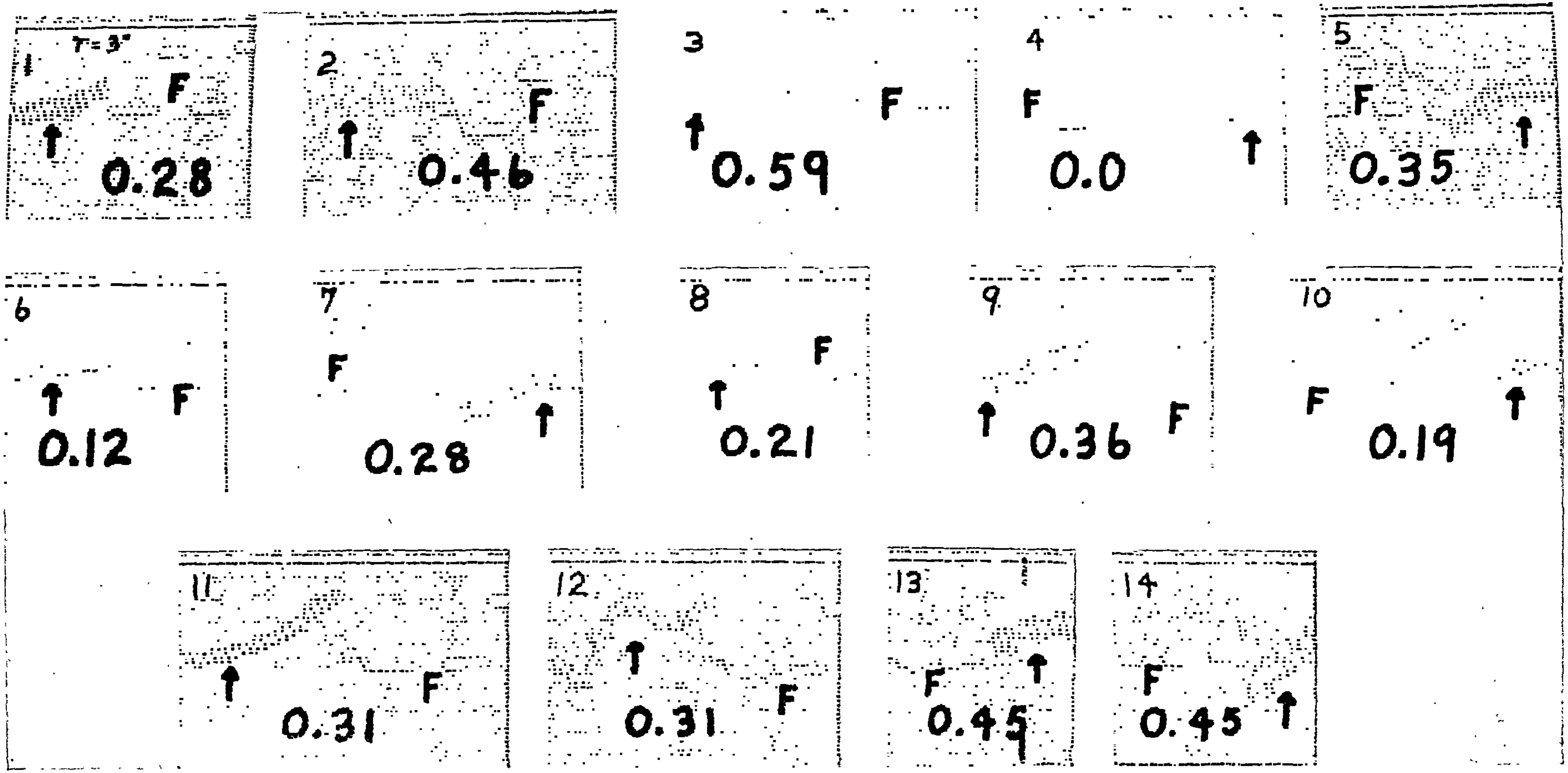

Fig. 5.—The photoelectrically recorded volume pulses in the various skin areas in a case of Raynaud's disease. Filter deflections at *F* and volume pulse measurements at the arrow. Filter equivalent of the volume pulse is written on each record. Upper row: pads of following fingers of right hand: *1*-index, *2*-middle, *3*-ring, *4*-little, *5*-thumb. Middle row: pads of following fingers of left hand: *6*-index, *7*-middle, *8*-ring, *9*-little, *10*-thumb. Lower row: skin of following: *11*-right forehead, *12*-left forehead, *13*-right nose, *14*-left nose.

A case of intermittent claudication, involving both legs, is presented in Table II. These data were obtained in late winter and early spring.

TABLE II

	2/15 26° C.	2/22 (2) 26° C.	2/22 (3)	3/1 24° C.	3/15 24° C.	3/29 (1) 28° C.
Right hand:						
Index finger	1.5	.67			1.0	
Middle finger	1.6	.89			2.0	
Ring finger	1.5	1.0			1.0	
Little finger	1.9	.65			1.0	
Thumb	1.3	.64			1.0	
Right foot:						
Big toe	.2	.2	.0	.3	.04	.75
Second toe	.3	.0	.16	.0	.06	.8
Third toe	.16	.14	.18	.41	.04	.75
Fourth toe	.25	.39	.51	.15	.08	.8
Fifth toe	.27	.22	.15	.18	.04	1.4
Dorsalis pedis	.0	.33	.11	--	.05	.53
Left foot:						
Big toe	.0	.0	.13	.1	.0	.28
Second toe	.21	.0	.0	.1	.0	.28
Third toe	.27	.0	.2	.0	.02	.37
Fourth toe	.2	.13	.2	.15	.05	.33
Fifth toe	.0	.17	.2	.1	.06	.5
Dorsalis pedis	.12	.15	.0	--	.0	.37

(1) Preceded by one week of warm weather. (2) Came from treatment in doctor's office. (3) One hour later.

Table II.—The arterial blood supply of the finger and toe pads, as indicated by the volume pulse amplitude in a case of intermittent claudication involving both thighs. The amplitude of the volume pulse is expressed in "filter" units. Male, aged 63; arteriosclerosis; blood pressure 150/105; dorsalis pedis pulse not palpable.

The subject rested in the laboratory for one hour preceding the determinations, except for the first (Feb. 22), which were made immediately after he arrived in the laboratory, and about thirty minutes after he had been treated with mecholyl iontophoresis. The continuation of poor blood supply to the toes despite treatment is in striking contrast to the effects of a week of warm weather preceding the last group of determinations (March 29). The greater response of the toe pads of the right foot agreed with the clinical impression that the circulation was better on this side. Intermittent venous occlusion was tried on this patient during one of his visits to the laboratory. The results were inconclusive (Table III), with the exception of the pulsations in the dorsalis pedis, which became detectable but were still very small. The changes in the toes were too small to be of any significance.

Mecholyl iontophoresis was tried in this case in the laboratory, fortunately at a time when the volume pulses in the toes were almost indetectable (Table IV). Iontophoresis was administered to both feet and calves. Conditions were ideal for demonstrating a dilator response. Some improvement in the right foot was shown by the increased volume pulse, but the changes in the left foot were too small to have any significance. Histamine iontophoresis in the laboratory, after a week of warm weather, increased the amplitudes of the volume pulses several times in the toes of the left foot, but the results on the right foot were

inconclusive, possibly because the toe vessels on this side were already considerably dilated. We do not know whether this was the maximal dilatation possible.

These therapeutic experiments are presented for their illustrative value, rather than as evidence of the efficacy of iontophoresis or of intermittent venous occlusion. It is obvious, however, that climate did more to open this patient's toe vessels than did the therapy. The experiments demonstrate that the method is capable of providing objective evidence concerning the state of the cutaneous circulation in patients, and is useful in estimating the immediate as well as the delayed effects of therapeutic procedures on the circulation in the treated areas.

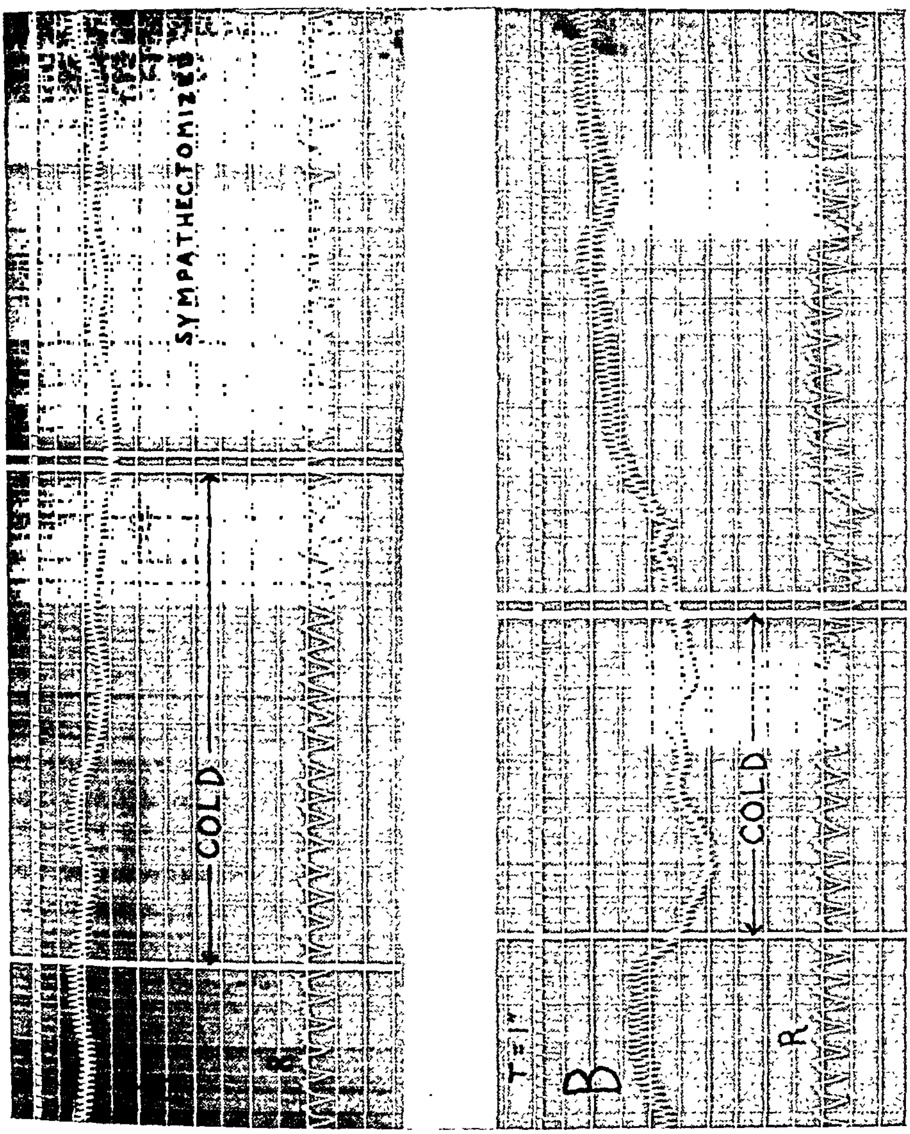

Fig. 6.—Reflex finger responses in a case of Raynaud's disease to cold stimuli applied to the opposite hand. *A*, response of sympathectomized finger. *B*, response of innervated finger. Immersion of opposite hand in ice water between vertical signals. Time: one second. Respiration by pneumograph.

This paper presents the applications of the photoelectric plethysmograph to the study of peripheral arterial reactions and to the estimation of the effects of various therapeutic procedures on the blood supply of

TABLE III

	2:00 to 2:15 23.8° C.	3:30 to 3:40 24° C.
Left foot:		
Big toe	.1	.1
Second toe	.1	.0
Third toe	.0	.13
Fourth toe	.15	.16
Little toe	.1	.2
Dorsalis pedis	.0	.1
Right foot:		
Big toe	.3	.2
Second toe	.0	.2
Third toe	.41	.2
Fourth toe	.15	.2
Little toe	.18	.26
Dorsalis pedis	.0	.14

Table III.—Effect of intermittent venous occlusion on the blood supply of the toes, as judged by the amplitude of the volume pulses (same patient as in Table II). Intermittent occlusion from 2:30 P.M. to 3:10 P.M.

TABLE IV

	RIGHT FOOT						LEFT FOOT					
TIME	BIG TOE	2ND TOE	3RD TOE	4TH TOE	5TH TOE	DORSALIS PEDIS	BIG TOE	2ND TOE	3RD TOE	4TH TOE	5TH TOE	DORSALIS PEDIS
1:50	.05	.06	.04	.08	.04	.0						
2:05							.0	.0	.02	.05	.07	.0
2:50	.14											
3:00	.19											
3:05	.27											
3:10	.25											
3:17	.38											
3:25-3:29	.27	.15	.22	.22	.42							
3:31-3:35							.0	.02	.03	.1	.1	
3:45						.13						.01

Table IV.—Effect of mecholyl iontophoresis to both legs and feet on the blood supply, as judged by the amplitude of the volume pulses of the toe pads (same patient as in Table II). Iontophoresis from 2:50 P.M. to 3:40 P.M.

the skin. The possibilities of this plethysmograph are not thereby exhausted. Its usefulness in distinguishing "active" from "passive" components and in separating arterial from venous reactions in the skin is described in another publication.[5] Under suitable circumstances, in which certain dynamic requirements are met, it appears to be possible to separate arterial reactions, venous reactions, and changes in flow in a skin area by means of the photoelectric plethysmograph. The possible application of this method to the study of disease is being investigated.

SUMMARY

The clinical application of photoelectric plethysmography is described. Its use in following vascular reactions, such as the spastic phenomena of Raynaud's disease, or in evaluating the completeness of sympathetic denervation of the skin, is indicated by selected examples. Its use in estimating the arterial blood supply of the skin of various areas is

illustrated on a normal subject, on a patient after sympathectomy, and after treatment with intermittent venous occlusion and iontophoresis in a case of intermittent claudication.

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Department of Clinical Reports

UNUSUAL CONFIGURATION OF THE HEART IN A CHILD

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THE common causes of abnormalities in the contour of the heart in children are congenital defects and rheumatic heart disease. As a result of the extensive studies which have been made, the nature of these changes is now fairly well understood. Rheumatic lesions can be diagnosed practically with certainty, and a reasonable assumption can be made in the commoner types of congenital abnormality. In the case described below there was an unusual, localized bulge on the left side of the heart. Its situation did not correspond to that of the changes in contour which are present in either of the above-named conditions.

CASE REPORT

A. J., a 13-year-old colored girl, was admitted to the Cardiac Clinic of the Kings County Hospital in January, 1938, with the chief complaint of palpitation and cough on exertion.

The previous history was irrelevant. She was born in Georgia, came to New York City at an early age, and, except for measles and pertussis, neither of which was severe, and occasional sore throats, had had no previous illness. The diet had been adequate and she was alert. There was no history of syphilis in the parents or child. There had been no genitourinary or gastrointestinal complaints, and there was no history of surgical or traumatic disease.

The present illness had commenced six months earlier, when she suffered from tonsillitis, and a nonproductive cough developed. There had been no elevation of temperature at any time. Since then she had had a slight hacking cough, but no fever, night sweats, weight loss, anorexia, posterior nasal discharge, or headache.

Physical examination revealed a well-nourished, well-developed 13-year-old negress, not acutely ill. There was no dyspnea, edema, cyanosis, or clubbing of the fingers. The pupils were equal and reacted to light and in accommodation. The ocular movements were normal, and the conjunctivae were free from icterus and petechiae. The fundi of the eyes were normal. Tonsillar tabs were present in the pharynx. The neck veins were not distended, and there were no palpable lymph nodes in the neck. The pulse rate was 96 and the blood pressure 132/92. The cardiac mechanism was normal. Examination of the heart revealed a marked, visible pulsation over the lower portion of the precordium, between the sternum and the nipple. The apex was palpated 11.5 cm. to the left of the midsternal line in the fifth intercostal space, outside the midclavicular line. No thrill was felt. At the apex a soft systolic murmur, transmitted to the axilla, was heard. This was constant on change of position, and extended throughout most of systole. With the heartbeat there was a clicking sound (like râles) in the region of the apex which extended to the midaxillary line. This was heard best with the patient in the recumbent position. The sounds at the base of the heart were of good quality, and the

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aortic second sound was equal in intensity to the pulmonic second. The lungs were negative on physical examination, as was the abdomen.

Laboratory Examination.—The blood Wassermann reaction was negative. The urea nitrogen content of the blood was 27 mg. per cent, the creatinine, 1.2 mg. per cent, and the sugar, 120 mg. per cent. The specific gravity of the urine was 1.025; the urine contained no albumin, sugar, or acetone, and was negative microscopically. The hemoglobin was 85 per cent, the erythrocyte count, 5,700,000, and the leucocyte count, 5,500; the differential leucocyte count showed 64 per cent polymorphonuclear leucocytes, 34 per cent lymphocytes, and 2 per cent monocytes.

I.

II.

III.

IV.

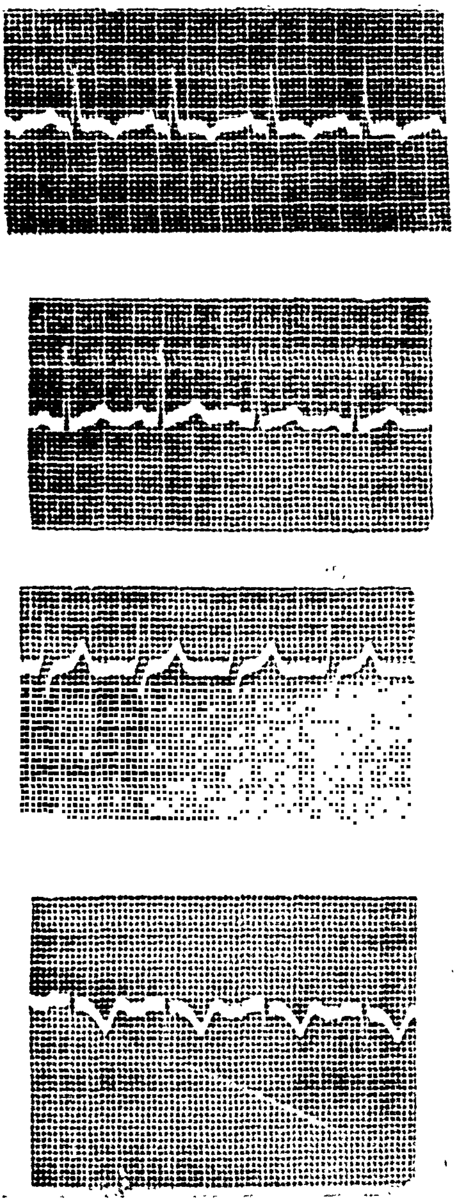

Fig. 1.—Electrocardiogram.

The electrocardiogram (Fig. 1) showed normal cardiac mechanism, a rate of 94, a P-R interval of 0.18 second, and a QRS of 0.08 second. The T wave was moderately inverted in Lead I. Leads II and III were normal. In Lead IV (method of Wolferth and Wood, right arm wire connected to precordial electrode, left leg wire to left leg electrode), the R wave was practically absent.

The teleroentgenogram (posteroanterior) showed a localized bulge at about the mid-portion of the left border of the heart (Fig. 2). In the right anterior oblique position (Fig. 3) the esophagram was normal, and the bulge was seen to protrude beyond the spinal column. The roentgenkymogram (Fig. 4) showed reversal of pulsation over the area of localized enlargement; this portion expanded when the rest of the ventricle contracted.

Fig. 2.—Teleroentgenogram (posteroanterior).

DISCUSSION

The outstanding features of this case were the protrusion of the left border of the heart, which showed reversal of pulsation in the roentgenkymogram; a diffuse, visible pulsation between the apex and the sternum; a systolic murmur at the apex, and, distinct from this, but in the same area, a clicking sound which was synchronous with the heartbeat.

The localized bulge in the left border of the heart suggested the following possibilities: (1) tumor of the heart, (2) diverticulum or congenital defect of the pericardium, and (3) aneurysm of the heart.

Fig. 3.—Teleroentgenogram (right anterior oblique).

TUMOR OF THE HEART

Yater[1] has recently reviewed the entire subject of tumors of the heart, and it is interesting to note that in the 143 cases of primary neoplasm of the heart that he collected, 117 of the tumors were benign and 26 malignant. The benign tumors were mainly myxomata, and most of the malignant tumors were sarcomas. He also pointed out that myxo-

mata usually arise from the endocardium of the left auricle in the region of the fossa ovalis, but occasionally from the valves. The majority of the sarcomas of the heart are situated in the auricles (more often the right, and frequently in the interauricular septum) and the pericardium. Thus, practically all primary tumors of the heart are intralocular, and could not give rise to the localized bulge which was present in this case. Secondary or metastatic tumors could be excluded by the absence of symptoms or signs of malignancy. Most heart tumors are solid, and their pulsation should be synchronous with the heartbeat, but the kymogram, in this case, revealed a reversal of pulsation in the protrusion. It is possible that a soft, very vascular tumor in the

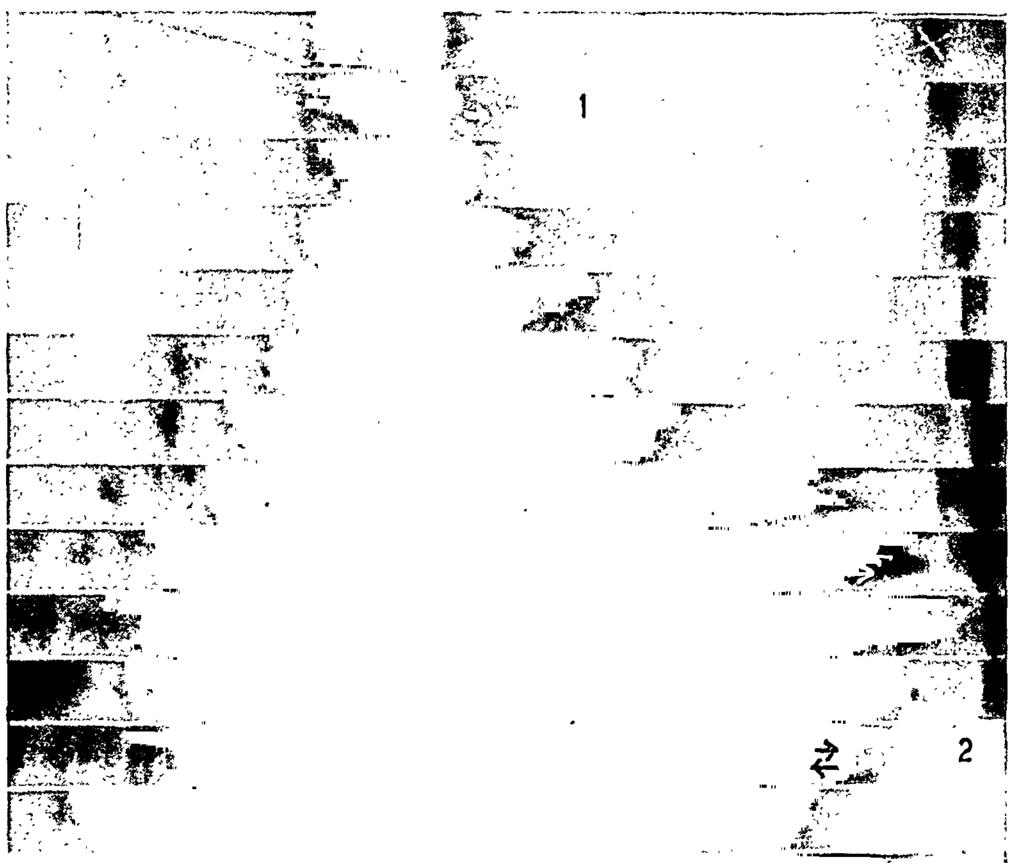

Fig. 4.—Roentgenkymogram. Ventricular pulsations may be accurately timed by comparing them with those in the descending aorta. Systole of the ventricle normally corresponds to expansion of the aorta. (1) The aortic waves. (2) The normal ventricular waves. (3) Reversal of pulsation over the involved area.

ventricular wall might so weaken it that not only would there be a bulge, but possibly also a reversal of pulsation. A tumor of the hemangiomatous type would be most likely to produce such an effect, but this tumor is very rare in the heart. In Yater's series, referred to above, there were only four cases, and in none of these was the tumor in the ventricular wall. Scott and Moore[2] reported a case of what was thought to be an aneurysm of the ventricle, but autopsy revealed a primary endothelioma invading the left ventricular wall and filling its lumen.

PERICARDIAL DEFECT

There are two main types of congenital defect of the pericardium. There may be complete absence of the pericardium, in which case the heart and lungs occupy a single cavity, or there may be a diverticulum of the pericardium. Both are rare. Abbott[3] has noted that when the pericardium is absent there is usually greatly increased mobility of the heart, occasionally hypertrophy without any of the usual etiologic factors, and, frequently, displacement of the heart to the left. A diverticulum is a thin-walled cyst, formed by the serous, or serous and fibrous, coats of the parietal layer of the pericardium, which communicates directly with the pericardial cavity. In our case, the strongest evidence against these possibilities was the fact that the roentgenkymogram showed reverse pulsations in the involved area.

ANEURYSM OF THE HEART

Finally there was the possibility of aneurysm of the heart. This is apparently an extremely rare condition in childhood. A review of the literature has revealed few reports of aneurysm of the heart at this time of life. In 1911, Herbert French[4] reported a case of traumatic aneurysm of the heart in a child of three, which resulted from a fall from a third-story window. She died twenty days following the accident, immediately after an anesthetic had been given for the reduction of a fracture. French assumed that the fall had caused a severe contusion of the heart, with hemorrhage into the myocardium, followed by softening, thinning, and, finally, rupture and hemopericardium. In 1920, Macfie and Ingram[5] reported three cases in native boys of the Gold Coast. There was no previous history of illness, and in all three sudden death occurred. The ages of the children were six, seven, and twelve; the condition was discovered at autopsy. The aneurysms were small and were located in the left ventricle near the apex of the heart (two were anterior, and one was posterior). The coronary arteries showed slight endarteritis, and they suggested that malarial endarteritis might have been an etiologic factor.

Criteria for the diagnosis of aneurysm of the heart have been suggested recently. These include the presence of a definite pulsation which is more marked between the apex and sternum than at the apex, and is associated with a muffled sound at this point. Since the advent of the roentgenkymogram it has been possible to ascertain whether the pulsations of all parts of the heart are synchronous. In cases of aneurysm, the sac expands during systole unless clot formation prevents it.

In this case, both the clinical and roentgenologic criteria for the diagnosis of cardiac aneurysm were fulfilled. In the absence of any other etiologic factor, such as trauma or coronary artery disease, and if the abnormal contour was caused by aneurysm, there must have been a congenital defect. The possibility that a soft tumor may have been infiltrating and weakening the cardiac muscle cannot be excluded.

SUMMARY

A case of localized protrusion of the left border of the heart in a twelve-year-old girl is described. The cause of this bulging was either a cardiac aneurysm of unknown etiology, possibly resulting from a congenital weakness of the muscle wall, or a soft vascular tumor of the myocardium. Both conditions are extremely rare, and a final diagnosis could not be made.

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SUBACUTE BACTERIAL (PARA-INFLUENZA) ENDOCARDITIS

A Case Report

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Subacute bacterial endocarditis is considered a clinical entity, characterized by chills, fever, cardiac murmurs, embolic phenomena, clubbed fingers, and enlargement of the spleen. Pathologically, one finds valvular vegetations superimposed on a scarred endocardium or a congenitally deformed valve. The *Streptococcus viridans* is so frequently the cause of subacute bacterial endocarditis that other organisms which might produce this condition are regarded as accidental invaders, or their presence is looked upon as evidence of unusual individual susceptibility. This is a study of the development of subacute bacterial endocarditis produced by the para-influenza bacillus.

REPORT OF CASE

History.—A colored man, aged 27, was admitted to the hospital in May, 1937, complaining of chills, fever, loss of appetite, and night sweats. The patient did not recall ever having had a rheumatic infection. He developed a genital lesion in 1933 and was treated for syphilis throughout 1934. He contracted gonorrheal urethritis in 1935. This disease had apparently been arrested. There was no history of illness during 1936. Three weeks before entering the hospital the patient began to have night sweats, felt weak, and lost his appetite. He also developed daily chills, associated with fever and drenching sweats. There were shortness of breath on exertion and frequent attacks of palpitation. Gradually becoming weaker, he was sent to the hospital. The patient's past history and family history were irrelevant.

Examination.—The patient was an acutely ill, undernourished, and dehydrated colored man; his temperature was 101.6° F., his pulse rate, 110, and his respiration rate, 20 per minute. The blood pressure was 160/70. The tongue was incrusted, and the teeth were in poor condition. The neck was not rigid. Occasionally, scattered râles were heard over the bases of the lungs. The heart was enlarged; the apex was in the fifth intercostal space, 12 cm. from the midsternal line. A diffuse impulse was noted over the entire precordium. A diastolic thrill could be felt over the aortic area. A systolic and a diastolic murmur were heard over the aortic area, and to the left of the sternum; they were transmitted downward. The pulse was regular, but of the Corrigan type, and pistol-shot sounds were heard over the femoral arteries. The liver and spleen could not be palpated. There was definite clubbing of the fingers. The deep and superficial reflexes appeared normal, and there were no signs of pyramidal tract disease.

Admission Laboratory Data.—The urine contained a trace of albumin; its specific gravity was 1.013; it was sugar-free; there were 4 to 5 leucocytes and 3 to 4 erythrocytes per high-power field. The erythrocyte count was 4,360,000, the hemoglobin, 89 per cent (Sahli), and the leucocyte count, 28,700; the differential count showed 83 per cent polymorphonuclear neutrophils, 14 per cent lymphocytes, and 3 per cent monocytes. The blood Wassermann and Kline reactions were negative. The nonprotein nitrogen content of the blood was 26 mg. per 100 c.c. The

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total blood protein was 4.9 grams, with 2.2 grams of albumin and 2.7 grams of globulin per 100 c.c. of whole blood. The patient's serum failed to agglutinate *Brucella abortus, Brucella melitensis, Pasteurella tularensis,* and *Bacillus proteus* X-19. A roentgenogram of the chest showed an "aortic type" of heart. The transverse diameter of the heart was 16.3 cm., and the transverse diameter of the thorax was 29.3 cm. The cardiothoracic ratio was 0.55.

Course in the hospital.—During the first ten days in the hospital the patient's temperature varied from 99 to 103° F., with frequent chills. The heart murmurs changed in pitch and quality from day to day; at times the diastolic murmur and thrill over the aortic area would be extremely harsh. On the eleventh day after admission the patient developed marked rigidity of the neck, and became very drowsy. At that time the deep reflexes were hyperactive, but there were no signs of pyramidal tract disease. Lumbar puncture revealed a yellow, turbid spinal fluid, under a pressure of 200 millimeters of water. The spinal fluid contained 104 leucocytes per c.mm., of which 89 were polymorphonuclear neutrophils and 11 lymphocytes. Blood cultures were taken on several occasions, and all revealed the para-influenza bacillus. The spinal fluid culture also developed a growth of para-influenza bacilli. The patient remained semicomatose; repetition of the blood studies during this terminal state revealed 3,150,000 erythrocytes, a hemoglobin of 40 per cent (Sahli), 13,150 leucocytes, 71% polymorphonuclear neutrophils, 1% eosinophils, 22% lymphocytes, and 1% monocytes. The patient succumbed three weeks after admission.

Clinical Diagnosis.—The clinical diagnosis was subacute bacterial (para-influenza) endocarditis and para-influenza meningitis.

AUTOPSY

The autopsy was performed by Dr. Paul Kimmelstiel, of the Department of Pathology, Medical College of Virginia.

The major pathologic changes were in the heart, lungs, and kidneys. There was an ulcerative, globular endocarditis of the aortic cusps, superimposed on an old, healed endocarditis. There were myocardial necrosis and embolic myocarditis. The kidneys were the seat of an acute, diffuse glomerulonephritis, with interstitial nephritis. There was an anemic (bland) infarct in the right kidney. The lungs revealed marked passive congestion.

The following are the details of the important pathologic changes.

Heart (Gross Description).—The heart weighed 550 gm. The right ventricular wall was 0.5 cm. in thickness. The left ventricular wall was 2.4 cm. in thickness. The epicardium was smooth and glistening; a few punctate hemorrhages were noted over the left ventricle. This ventricle was markedly injected, particularly over the left anterior portion and the base. The endocardium was smooth except for an area to be mentioned later. The pulmonary cusps and the mitral and tricuspid valves were intact. There was no thickening of the chordae tendineae or of the free edge of the visible leaflets. All three aortic cusps showed marked thickening of the free margins, which were rolled. The aortic cusps were contracted. The process of fibrous thickening involved the tissue of the commissures and encroached a few millimeters upon the aorta. Coarse verrucous vegetations were noted around the corpora arantii of *the posterior cusp.* The right aortic cusp was covered by a soft irregular mass of globular vegetation, measuring 2 by 1 by .08 cm. This mass was firmly adherent to the free margin of the valve and was floating freely. Just beneath the base of the vegetation there was a ragged ulceration of the aortic cusp, measuring 0.5 cm. in diameter. Both ventricles, particularly the left, were enlarged. The apex of the left ventricle was rounded. The papillary muscles were flattened, and the hypertrophy of the wall was confined to the left ventricle. The myocardium was

of a mottled, maroon color, and there were a few hemorrhages on its cut surface. In the upper, posterior portion of the interventricular septum there was an area 2.5 cm. in diameter, in which the wall was thinned; the endocardium covering it had a grayish appearance. There was slight atherosclerosis of the first part of the aorta and the coronary arteries. The coronary arteries were patent throughout.

Heart (Microscopic Description).—There were two types of changes in the sections of the heart. The first consisted of multiple, small, scattered foci of early myocardial necrosis. There was only a moderate reaction of polymorphonuclear leucocytes. These were considered as ischemic foci, caused by emboli in the smaller branches of the coronary arteries. The second type of reaction consisted of numerous smaller foci, composed of accumulated polymorphonuclear cells in areas in which the myocardium was partially or completely destroyed by liquefactive necrosis. These foci were very small and not well defined. A larger branch of the left coronary artery was the seat of an acute panarteritis, with complete destruction of the wall in one segment and diffuse infiltration of all layers by polymorphonuclear leucocytes and round cells of various types. This vessel contained a thrombus which was attached to its wall and was composed of fibrin, platelets, and polymorphonuclear cells. The myocardium was edematous, particularly throughout the perivascular trabeculae. Round cell infiltration, composed of lymphocytes and a few round cells, was seen in scattered areas beneath the endocardium.

Kidney (Microscopic Description).—Acute interstitial nephritis, associated with an early, diffuse glomerulonephritis, was noted. These changes were intracapillary in character and consisted mainly of endothelial proliferation and polymorphonuclear leucocytes within the capillary tufts. The anemic infarct was not unusual.

DISCUSSION

The para-influenza bacillus might be considered a hybrid, in the sense that it is an atypical hemolytic organism which so closely resembles hemophilus influenzae that the only differentiating features are that it requires a V factor rather than an X factor for growth, and is able to ferment maltose, saccharose, and often dextrin (Topley and Wilson[1]). It is now believed that many old recorded cases of hemophilus influenzae invasion of the endocardium were really para-influenzal in origin, because, prior to recent studies (Miles and Gray[2]), the V and X factors were not used for differentiation. There is no clinical reason for distinguishing between these hemolytic organisms, for, if they invade the endocardium, the typical syndrome of subacute bacterial endocarditis is produced. Our case was not unusual in this respect, for the clinical course was typical of subacute bacterial endocarditis.

Neither the clinical features nor the pathologic changes differ significantly from those of *Streptococcus viridans* infection. Many observers agree on this point (Horder,[3] Oppenheimer,[4] Thayer,[5] Russell and Fildes[6]). The embolic spread to the central nervous system is not unusual in subacute bacterial endocarditis (Toone[7]). A definite meningitis was recognized very early in our case.

SUMMARY

A case of infective endocarditis caused by a para-influenza organism is described. Clinical, post-mortem, and bacteriological observations

confirmed the diagnosis. This case does not differ from the usual type of subacute bacterial endocarditis.

REFERENCES

1. Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, Ed. 2, Baltimore, William Wood and Company, 1936.
2. Miles, A. A., and Gray, J.: Haemophilus Para-Influenzae Endocarditis, J. Path. and Bact. 47: 257, 1938.
3. Horder, T. J.: Infective Endocarditis, Quart. J. Med. 2: 289, 1908-09.
4. Oppenheimer, E. H.: A Case of Influenza Bacillus Endocarditis, Bull. Johns Hopkins Hosp. 38: 372, 1936.
5. Thayer, W. S.: Bacterial or Infective Endocarditis, Edinburgh Med. J. 38: 237, 1931.
6. Russell, D. S., and Fildes, P.: A Case of Endocarditis in Man Associated with Bacillus Para-Influenza, Rivers, 1922, J. Path. and Bact. 31: 651, 1928.
7. Toone, E.: Personal Communication.

Department of Reviews and Abstracts

Selected Abstracts

Leo, Sidney D., Prinzmetal, Myron, and Lewis, Harvey A.: *Observations Upon the Pressor Substance Causing the Rise in Blood Pressure Following the Termination of Temporary, Complete Renal Ischemia.* Am. J. Physiol. 131: 18, 1940.

The previous injection of piperidomethyl-3-benzodioxane (933F) does not prevent the rise in blood pressure which results from the re-establishment of the circulation in the completely ischemic kidney, proving that the substance responsible for this rise is not of an epinephrine-like nature.

The pressor reaction which follows the termination of complete renal ischemia is greatly reduced or abolished in animals rendered tachyphylactic to renin. This proves that the substance causing the rise in blood pressure is renin or a pressor principle having similar properties of tachyphylaxis.

The pressor effect of extracts of completely ischemic kidneys is greater than that of extracts of control normal kidneys.

AUTHORS.

Hausner, Erich, Essex, Hiram E., Herrick, J. F., and Baldes, Edward J.: Control of Coronary Blood Flow in the Heart-Lung Preparation. Am. J. Physiol. 131: 43, 1940.

In the heart-lung preparation the influence of various factors on coronary flow was studied with the thermostromuhr. In agreement with others an intimate dependence of coronary flow on mean arterial blood pressure was found. Changes in cardiac output had no effect on coronary flow, if the arterial pressure and the temperature of the perfusing medium were kept constant. Stimulation of the cardiac branches of the stellate ganglion of the heart-lung preparation augmented coronary flow on an average of about 150 per cent. Similar values for coronary flow were obtained in the presence of a constant arterial blood pressure. The increase in coronary flow resulting from stimulation of the sympathetic nerves of the heart-lung preparation is thought to be due at least in part to a vasodilator action of the sympathetic nerves. An augmentation of coronary flow was demonstrated with acceleration of the heart rate by means of an electric stimulator. The augmented coronary flow was not due to an elevated mean blood pressure.

AUTHORS.

Asmussen, Erling: The Cardiac Output in Rest and Work in Humid Heat. Am. J. Physiol. 131: 54, 1940.

Acclimatization to humid heat seems to involve such regulations that the circulation in rest and during work in a steady state can be kept at a practically normal level. A blood volume increased by about 5 per cent, and a slightly higher pulse rate are assumed to be the two main factors in this regulation. Circulatory

failure during work develops rather fast in humid heat owing to the fact that the heat dissipation is made difficult. A larger amount of blood is demanded for the skin circulation, making maintenance of an adequate cardiac output increasingly difficult.

AUTHOR.

Reimann, Hobart A.: Hypothermia. Subnormal Temperature and Its Relation to Neurocirculatory Asthenia (Soldier's Heart). J. A. M. A. 115: 1606, 1940.

Nine patients were studied whose temperature level was consistently subnormal. Besides hypothermia they usually had other signs and symptoms of vagotonia such as hypotension, bradycardia, palpitation, sweating, low basal metabolic rates, and numerous bizarre complaints for which no organic basis could be found. The symptoms and signs manifested by these men are the same as those described in the conditions known as neurocirculatory asthenia, effort syndrome, or soldier's heart and probably arise from similar causes. Unless patients of this type are given a correct diagnosis they may be subjected to much needless investigation and treatment and may be assigned to tasks beyond their limitations during military service. After possible organic causes for their disorder have been ruled out, treatment along psychotherapeutic and physical therapeutic lines is helpful.

AUTHOR.

Moia, Blas: The High R_3 Wave in Electrocardiogram With Ventricular Complexes of Left Type. Rev. argent. de Cardiol. 7: 129, 1940.

One hundred electrocardiograms were analyzed in which the QRS_3 of the left type not exceeding 0.10" in duration, showed an R wave of high voltage, greater than the 25 per cent of the highest wave. A study was made of the other leads and the electrocardiographic findings were correlated with clinical conditions.

When this abnormality coincided with an R_1 wave of low voltage (with or without Q_1, without a marked S_1) sensibly lower than R_2 or when it was higher than R_2, all the patients showed cardiovascular alterations.

It was found that in certain conditions the percentage of cases with clinical signs of coronary insufficiency was very high: 77.77 per cent, when R_1 was of low voltage and much lower than R_2 (type of Q_1 of Wilson et al.); 71.42 per cent when R_3 was of unusual height, equal to the deep S_3 wave (plus minus complexes of Katz et al.); 50 per cent when R_2 of small height was accompanied by deep S_2 wave; and 22.97 per cent when there was only a left axis deviation with no other modifications.

It is pointed that the 22.23 per cent of the Q_1 classical type without a marked S_1 is observed in cases of rheumatic carditis with aortic insufficiency and coexistent mitral disease, and that, contrary to the observations of Katz et al. the wide diphasic complex was found to correspond to congenital heart disease in only 28.58 per cent of cases.

The existence of characteristic modifications of Lead III and their close correlation with clinical signs of coronary insufficiency give diagnostic value to the anomaly described.

The pathologic significance of triphasic complexes with high R_3 is discussed and the influence of respiratory movements on R_3 wave are analyzed.

AUTHOR.

Öhnell, Richard F.: Post Mortem Examination and Clinical Report of a Case of the Short P-R Interval and Wide QRS Wave Syndrome. Cardiologia 4: 249, 1940.

I have presented the pathologic anatomy and other data from a case of the type, the clinic of which was described by Wolff, Parkinson, and White in 1930.

Our patient succumbed suddenly to a heart attack. In the myocardium, round cell infiltration (one of the foci bordering the left ventricular branch of the A-V bundle) and an increased amount of connective tissue and brown atrophy were microscopically found. The theories proposed for the WPW syndrome are discussed and a special type of coupled ventricular premature beats are suggested as an explanation.

AUTHOR.

Scherf, David, and Weissberg, Jonas: The Electrocardiogram After Intravenous Injection of Hypertonic Sucrose and Saline Solutions. Cardiologia 4: 260, 1940.

Hypertonic sucrose and saline produce definite electrocardiographic changes in the majority of patients with angina pectoris. In view of the fact that precordial pain frequently develops in such patients after the intravenous injection of these solutions, it may be assumed that the reason for the electrocardiographic changes and the pain is a relative myocardial ischemia immediately after the introduction of these solutions into the general circulation. The action of these hypertronic solutions consists of an increase in blood volume without a comparable increase in myocardial blood supply. This is the consequence of an osmotic action.

AUTHORS.

Dressler, Wilhelm, and Pfeiffer, Robert: Cardiac Aneurysm. A Report of Ten Cases. Ann. Int. Med. 14: 100, 1940.

Ten cases are reported in which the diagnosis of cardiac aneurysm was made during life. In two of these cases the diagnosis was verified by post-mortem examination, while five cases characteristic radiologic findings were obtained.

The diagnosis of cardiac aneurysm is based primarily on physical examination. On palpation one finds a large and forceful cardiac thrust, which, depending upon the site of the aneurysm, is located either within the mid-clavicular line or outside of it, and most commonly at the level of the fifth rib. The diffuse character of the thrust, its considerable width, and particularly its medial extension, are significant features in diagnosis. The area of pulsation is likely to be situated more craniad than one would expect for the apical thrust caused by an hypertrophied left ventricle. Such a pulsation is of significance for the diagnosis of cardiac aneurysm, if the history and the electrocardiographic findings indicate a preceding cardiac infarction, and if other causes for such a forceful cardiac thrust, such as hypertension or mitral and aortic valvular lesions, can be excluded. It is especially significant if the development of such a pulsation can be observed subsequent to a coronary artery occlusion.

In our material we have not observed murmurs nor any particular findings obtained by means of percussion.

The radiologic examination revealed characteristic features in only half of our cases. This should be explained by the fact that the aneurysmal development is most often limited to the apical portion of the heart. This location results merely in an elongation of the apical portion of the silhouette, such a finding being not characteristic in any way. Pathognomonic findings in the roentgenogram, however, may be expected for those cases where the aneurysmal formation involves the basal or middle portions of the left ventricle. One may then expect to find along a part of the left lower cardiac contour one or the other of the following findings: a localized bulge, a sudden kink, a centrifugal, systolic pulsation, calcification, shell-like in arrangement. The esophagus may reveal in its lower third either an impression from in front or a shallow deviation dorsad.

Electrocardiographic alterations indicating cardiac infarction were well marked in all of our cases and remained unchanged over a course of years. A deep S deflection in Leads II and III was strikingly noted in one-half of the cases.

The prognostic outlook in the presence of cardiac aneurysm is relatively favorable. This refers both to expectation of life and to effort capacity.

AUTHORS.

Graham, H. Boyd: Rheumatic Heart Disease. M. J. Australia 2: 101, 1940.

A classical description of rheumatism in childhood is presented in the form of extensive extracts from Cheadle's Harveian Lectures of 1889.

Additional features of outstanding importance are outlined; they have been added to our knowledge of the subject since Cheadle's time.

It is advanced as a plausible theory, arrived at by inference from other workers' published results, that the initial hemorrhagic lesions of rheumatic affections lead to reactionary developments which comprise the general and special pathology of the disease.

AUTHOR.

Brown, Morton G., and Wolff, Louis: Recovery From Acute Rheumatic Fever Without Permanent Cardiac Damage. New England J. Med. 223: 242, 1940.

Fifty per cent of a group of 175 patients with acute rheumatic fever showed no evidence of heart disease after follow-up periods averaging seven years.

There is no constant relation between the severity of the illness or the number of recurrences and the development of cardiac damage.

Patients who show no permanent organic heart changes following the first attack of rheumatic fever are prone to escape permanent injury despite further attacks.

The final evaluation of the state of the valves must be delayed for several years after an attack of rheumatic fever.

AUTHORS.

Swift, Homer F.: Public Health Aspects of Rheumatic Heart Disease. Incidence and Measures for Control. John H. Wycoff Lecture for 1939-40, J. A. M. A. 115: 1509, 1940.

The size of the problem of rheumatic heart disease, from the standpoint of public health, indicates the desirability of widely extending the facilities for meeting the situation. The long period usually consumed in the evolution of rheumatic heart disease offers opportunity for interfering with that evolution at various times. Those unfavorable factors classified as economic are subject to improvement. Favorable climatic factors may be utilized. Because functional trauma of cardiac tissues harboring rheumatic inflammation probably increases the damage to these tissues, prolonged rest for such actively diseased structures is requisite and should be provided on a scale commensurate with the size of the problem. The role of hemolytic streptococcus infections in initiating the disease rheumatic fever and in inciting relapses indicates the importance of protecting these patients from such infections. When these elements in a public health program are clearly recognized, there can be little doubt of its establishment.

AUTHOR.

Kuttner, Ann G.: The Effect of Large Doses of Vitamins A, B, C and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children. J. Clin. Investigation 19: 809, 1940.

No evidence was obtained to suggest that the addition of large doses of vitamins A, B complex, C, and D to an ordinary well-balanced diet reduces the incidence of upper respiratory infections.

Three children who had received the additional vitamins for a considerable period of time developed rheumatic symptoms following an attack of streptococcus pharyngitis.

Children on the regular diet without additional vitamins and those on the regular diet with additional vitamins gained weight at approximately the same rate during the five-month period.

AUTHOR.

Roth, Irving R.: Clinical Aspects of Rheumatic Fever in Adults. Bull. New York Acad. Med. 16: 514, 1940.

Rheumatic fever in adults does not seem to conform to a distinctive pattern, and the polyarthritic picture suggested by hospital records is more apparent than real. At any rate, it does not represent the whole disease. Smoldering forms are not uncommon and it is this form that probably precipitates insidious failures of the circulation. It is probably responsible also for auricular fibrillation in some cases.

The anatomic lesions in the younger adults are generally multiple but, as age advances, those with combined mitral and aortic lesions are seemingly weeded out. Chances for survival seem best for those who have mitral lesions alone.

Auricular fibrillation, except as a terminal event, is rare in early adulthood. However, as age advances, it soon becomes the dominant arrhythmia and may be present in from 20 to 25 per cent of patients past 40 years of age.

Functional capacity in young adults is generally excellent despite multiple valvular lesions. At middle age or beyond, it is on the decline and heart failure is an ever-present threat.

Accompanying diseases are of minor importance in the younger adult with a rheumatic cardiac condition. The greatest hazard is an acute rheumatic episode. At middle age, on the other hand, an accompanying hypertension seems to be the most embarrassing complication.

Emotional factors are present in both groups and color the clinical picture appreciably. Not only symptoms but also physical signs and, in a measure, even prognosis are influenced by them. They must be taken into serious account in any attempt to appraise the clinical aspects of rheumatic heart disease in adult life.

AUTHOR.

Kampmeier, R. H., and Combs, Stuart R.: The Prognosis in Syphilitic Aortic Insufficiency. Am. J. Syph., Gonor. & Ven. Dis. 24: 578, 1940.

An analysis has been made of 163 cases of syphilitic aortic insufficiency studied at Vanderbilt University Hospital. One hundred and twenty, or 73 per cent, of the patients are dead; 54.6 per cent of the deaths occurred within three years after the onset of symptoms.

The importance of race and sex in the prognosis of syphilitic aortic insufficiency is clearly indicated by this study. Only one-fourth of the negro males with syphilitic aortic insufficiency survived three or more years after the appearance of symptoms, whereas slightly less than one-half of the white males and negro females, and over one-half of the white females survived three or more years.

Occupations involving manual labor are conducive to poor prognosis in syphilitic aortic insufficiency.

As is to be expected, the chance finding of asymptomatic syphilitic aortic regurgitation at the time of initial examination occurred more frequently in patients who are still living.

Moreover, the presence of congestive heart failure and evidence of free aortic regurgitation was noted more frequently in patients who experienced, subsequently, short survival periods.

The longer the duration of symptoms of syphilitic aortic insufficiency before the diagnosis becomes established, the poorer the prognosis.

This study does not indicate that adequate antisyphilitic treatment influences favorably the prognosis of syphilitic aortic insufficiency.

AUTHORS.

Ayman, David, and Goldshine, Archie D.: Blood Pressure Determinations by Patients With Essential Hypertension. I. The Difference Between Clinic and Home Readings Before Treatment. Am. J. M. Sc. 200: 465, 1940.

Thirty-four patients with various degrees of essential hypertension had their blood pressure studied over a long period in the clinic and at home. The home readings have been taken very carefully twice daily for weeks or months by the patient or a member of the household. This study shows that the home systolic and diastolic blood pressure readings are lower than the clinic readings in all cases of essential hypertension. In 30 per cent of the cases the systolic home blood pressure readings were 40 mm. or more lower than those in the clinic, and in 24 per cent the diastolic home readings were 20 mm. or more lower than the clinic readings. The method caused no neurosis or harm in any patient. Those patients with only slight difference between home and clinic readings had, in general, comparatively little fluctuation of blood pressure from day to day. The home blood pressure method should be of value to teach the patient the nature of his disease, to help the physician observe better the natural course of the disease, to aid in the prognosis of the individual case, and to permit the clear-cut evaluation of therapy.

AUTHORS.

Saphir, Otto, and Ballinger, Joseph: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis. Arch. Int. Med. 66: 541, 1940.

Three cases of severe arterial hypertension secondary to unilateral renal vascular stenosis, with consequent ischemia of one kidney, are reported. In two of these, autopsy revealed unilateral malignant nephrosclerosis (arteriolonecrosis). Because of recent experimental evidence, this unique observation could be explained readily. From his experimental studies, primarily concerned with the production of arterial hypertension by clamping the renal arteries in the dog, Goldblatt concluded that both hypertension and renal insufficiency are the minimal prerequisites for the induction of arteriolonecrosis, for in the absence of either of these factors no necrotizing changes are observed. The patients in both these cases had severe arterial hypertension brought about by renal artery changes, with resulting ischemia of one kidney. Both subsequently had renal excretory insufficiency. This was precipitated in one instance by the onset of congestive heart failure and in the other by the development of acute ascending pyelonephritis in the kidney opposite the ischemic one. Because of the presence of the severe arterial hypertension and excretory renal insufficiency, the arterioles in the contralateral kidneys (with a patent vascular system) showed necrotic changes, and these kidneys presented the typical picture of malignant nephrosclerosis. The arterioles in the ischemic kidneys revealed no necrotic changes because the stenosis of the renal and intrarenal arteries militated against the presence of severe hypertension within the arterioles. Thus, the pathogenesis of the malignant nephrosclerosis in these cases is exactly similar to that of the arteriolo-

necrotic changes produced experimentally by Goldblatt. The third case was included in this report for comparative purposes. This patient died of intercurrent bronchopneumonia and never showed evidences of renal insufficiency. In this instance the requisite factors for development of the malignant phase of hypertension were lacking, and, as was expected, there was no evidence of arteriolonecrosis on post-mortem examination.

AUTHORS.

Odel, Howard M.: Structural Changes in the Arterioles of the Myocardium in Diffuse Arteriolar Disease With Hypertension Group 4. Arch. Int. Med. 66: 579, 1940.

The results of this study indicate that, in the presence of diffuse arteriolar disease with hypertension group 4, structural changes in varying degrees of severity occur in the arterioles of the myocardium.

Wide variation from case to case was noted in the nature and degree of change. Increase in the medial nuclei seemed to be an early change, with hyperplasia of the internal elastic lamina, intimal proliferation, and degenerative changes occurring later in the process. It is a significant fact that structural changes in the myocardial arterioles were not observed in all cases and that, when they did occur, the changes were similar to those occurring in other organs in the same case, although less pronounced.

The analysis of the clinical features in this series of cases indicates that the syndrome of malignant hypertension is a clear-cut clinical entity and that the clinical picture may be characterized by symptoms predominantly cerebral, cardiac, or renal, or by any combination of the three.

Not only was there wide variation in the occurrence and degree of severity of the histologic changes among individual patients, but there was a striking difference in the degree of involvement between different vessels of the same patient and between different segments of the same vessel.

From the evidence presented here from data collected by others, it appears that malignant hypertension is a diffuse arteriolar disease in every sense of the term and that no organ which is subjected to elevation in systemic blood pressure can escape entirely. Why structural changes in the arterioles of the myocardium do not progress at the same rate or to the same degree as do similar changes in the arterioles of other organs is a question which has yet to be answered.

AUTHOR.

Hildebrand, Alice G., Montgomery, Hamilton, and Rynearson, Edward H.: Necrobiosis Lipoidica Diabeticorum. Arch. Int. Med. 66: 851, 1940.

Seventy-eight cases of necrobiosis lipoidica diabeticorum which have been described in the literature since the first report of this dermatosis by Oppenheim, in 1929, are reviewed. Observations on eight cases of necrobiosis lipoidica diabeticorum encountered at the Mayo Clinic since 1936 are related. More than 87 per cent of all the patients, both those seen elsewhere and those seen at the clinic, had diabetes mellitus, and in eight typical cases of necrobiosis, evidence of diabetes mellitus was not found. In the majority of the cases in the entire series, the cutaneous lesions had developed from several months to as long as seventeen years after the onset of diabetes, although in about 18 per cent of the cases encountered elsewhere and 25 per cent of those encountered at the clinic the reverse was true, the cutaneous lesions preceding the onset of the diabetes by as long as eight years. All patients were white, and more than 80 per cent were women. The most common age of onset among all patients was between 10 and 40 years.

In those who had diabetes mellitus, the constitutional disease in most instances could be called moderately severe to severe, and in most of them the diabetes had been poorly controlled. Trauma apparently played a definite role in the development of the cutaneous lesions in several cases.

The lesions in this condition are most often reddish papules or yellowish plaques with well-defined reddish-brown borders, much infiltration, and central telangiectasia. They usually occur on the lower parts of the legs. Microscopically the lesions are characterized by changes in the deep layers of the cutis, consisting of necrobiotic regions in which there are granular degeneration of the collagen fibers, loss of elastic fibers, and extracellular deposition of various lipoids, surrounded by a region in which the arterioles show intimal proliferation and perivascular myocytic infiltration. The absence of xanthoma or foam cells containing cholesterol and cholesterol esters differentiates these lesions from those of the other xanthomatoses except lipoid proteinosis, which represents a different clinical picture. Quantitative determinations of the lipoid constituents of these lesions were suggestive of a relative increase of lecithin in the tissues.

Studies of the blood lipoids have shown that in the majority of all cases encountered elsewhere and in all of the cases encountered at the clinic the values lay within normal limits. The lesions tended to run a chronic course, and neither local therapy nor, in the case of diabetic patients, general management tended to speed their healing. In some cases the lesions slowly receded and left depressed scars.

Two ideas regarding the pathogenesis of this condition have been considered: (1) that which assumes the occurrence of a primary vascular injury, possibly by circulating toxins, with secondary thrombosis, necrosis, and fat imbibition; and (2) that which assumes a local lipoid disturbance in the skin, based on a general disturbance in fat metabolism. Neither hypothesis has proved satisfactory in the light of studies made both here and elsewhere. Therefore, the pathogenesis of this condition remains obscure.

AUTHORS.

Ravenna, Paolo: Banti Syndrome (Fibrocongestive Splenomegaly): Definition, Classification and Pathogenesis. *Arch. Int. Med. 66: 879, 1940.*

Evidence has been accumulating which supports the view that Banti splenomegaly is largely due to splenic congestion and that this congestion is not dependent on an obstructive factor in the portal-venous bed. It is suggested that the congestion may be due to primary lesions of the small splenic arteries which regulate the blood flow into the spleen ("primary active congestion").

The human spleen should be considered as an elastic rather than a contractile organ. Its variations in size depend on variations in volume of the inflowing blood, rather than on active contractions of the smooth muscle of its supporting framework.

From a mechanical point of view, the spleen might be defined as an automatic controller which regulates the pressure of the splenic venous blood in order to maintain the balance between the volume of inflowing blood and the amount which can be discharged through the hepatic resistance. Normally, and within certain limits, in pathologic conditions, the splenic elasticity guarantees a pressure sufficient to secure the further progress of venous portal blood. Congestive splenic enlargement is therefore a mechanism to counterbalance either increased volume of portal blood or increased peripheral resistance to the discharge of a normal amount of blood.

The Banti syndrome is a symptom complex dominated by chronic fibrocongestive splenomegaly, accompanied by portal hypertension and complicated by,

or associated with, hepatic cirrhosis or thrombosis of the splenic and portal veins. It may depend on various causative agents, either infective or toxic. A scheme for its etiological classification is presented.

The splenic changes of the Banti syndrome are probably due to primary lesions of the splenic arterioles, the regulating power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondarily, hepatic cirrhosis and venous thrombosis may aggravate the state of portal circulation.

AUTHOR.

Levitt, Abel, and Levy, Dexter S.: Luetic Meso-Aortitis With Aneurysm of the Thoracic and Abdominal Aorta. Am. J. Clin. Path. **10:** 332, 1940.

A case of vascular syphilis is reviewed in which there was an unusually large thoracicoabdominal aneurysm. This aneurysm apparently developed about twenty years after the primary lesion, progressed rather rapidly in its last year to involve the spinal cord by pressure, and finally terminated by rupture into the peritoneal cavity.

AUTHORS.

Ronald, James, and Leslie, Margaret: Thrombosis of the Abdominal Aorta. Glasgow M. J. **84:** 7, 1940.

A case of complete thrombosis of the abdominal aorta is reported. The condition was unaccompanied by localizing signs, and occurred in a man aged 43 years who was the subject of hypertensive and syphilitic disease.

Of particular interest in this case was the almost complete lack of "regional" signs and symptoms. Apart from the sudden acute abdominal pain and the gripping feeling in the legs, there was little to distinguish it from any other case of severe hypertension. Although autopsy failed to reveal the establishment of a collateral circulation, there was no clinical evidence of impaired circulation in the extremities. It is difficult to understand how such an extensive lesion as was present in the aorta can be unaccompanied by localizing signs.

AUTHORS.

LeRoy, George V., and Speer, John H.: A Comparison of the Coronary Vasodilator Activity of Certain Alkyl Xanthines. J. Pharmacol. and Exper. Therap. **69:** 45, 1940.

The activity of a series of newly conceived xanthine derivatives has been investigated, using the outflow of blood from the coronary sinus of an intact, anesthetized dog as an indicator. The results of the study of these drugs are reported.

Sodium salts of three of the new compounds: 1,3, dimethyl, 8, ethyl xanthine; 1,3, diethyl, 8, methyl xanthine; and 1,3, diethyl xanthine, augment the coronary sinus outflow to an extent that exceeds the increase observed when sodium salts of theophylline and theobromine are employed.

It is demonstrated, but not explained, that the ethylene diamine salt of theophylline is twice as active as the sodium salt. For theobromine, the difference is even greater; and the sodium acetate compound is five times as effective as the sodium salt. The coronary vasodilator effectiveness of the experimental sodium salts of the alkyl xanthines studied is inferior to the activity of the familiar therapeutic compounds, theophylline ethylene diamine, and particularly, theobromine sodium acetate.

AUTHORS.

Grollman, Arthur, Harrison, T. R., and Williams, J. R.: Therapeutics of Experimental Hypertension. J. Pharmacol. and Exper. Therap. 69: 76, 1940.

The effect of sodium nitrite, potassium thiocyanate, erythrol tetranitrate, *Allium sativum*, acetyl-β-methylcholine, sodium chloride, and renal extract on the blood pressures of hypertensive rats was investigated. The blood pressure was reduced to normal levels following the administration of renal extract. None of the so-called "depressor" or "hypotensive" substances manifested an ability to reduce appreciably the blood pressure, and their clinical value is thus questionable. The administration of a relatively large dose of sodium chloride did not markedly elevate the blood pressure.

AUTHORS.

Gottdenker, F., and Wachstein, M.: Circulatory Effects of the Venom of the Indian Cobra (Naia Naia). J. Pharmacol. and Exper. Therap. 69: 117, 1940.

In cats and rabbits the intravenous injection of a small dose of cobra venom (6 to 9μ grams per kilogram) causes a long lasting rise of arterial blood pressure, occasionally preceded by an evanescent depressor effect. When the blood pressure has returned to normal the injection of a second similar dose of venom is ineffective (tachyphylaxie).

Cobra venom causes vasoconstriction in the rabbit's ear perfused with physiologic salt solution and there is no, or only little, diminution of the effect by repeated administration of the venom.

In the heart-lung preparation of the dog the injection of cobra venom (60μ grams) produces long lasting dilatation of the coronary vessels which can readily be desensitized against the venom by a previous injection of a subthreshold dose.

The intravenous injection into cats of 9μ grams of cobra venom per kilogram produces profound alterations in the electrocardiogram.

Cobra venom causes systolic standstill of the auricular strip (rabbit's and guinea pig's heart) and of the fiber of Purkinje (dog's heart). No tachyphylaxie could be obtained in these preparations.

In the isolated frog's heart cobra venom causes irreversible systolic contracture. During the development of the contracture the electrocardiogram shows signs of impairment of conduction, shortening of the duration of the systole and changes in the QRS complex and T wave. The absence of calcium ions in the perfusion fluid alters the response. The muscle becomes less sensitive to the venom which produces stoppage of beat without signs of systolic contracture.

AUTHORS.

Gold, Harry, Kwit, Nathaniel T., and Cattell, McKeen: Studies on Purified Digitalis Glucosides. I. Potency and Dosage of "Digitaline Nativelle" by Oral Administration in Man. J. Pharmacol. and Exper. Therap. 69: 177, 1940.

Digitalis leaf was compared with "Digitaline Nativelle" in a selected group of forty-nine patients, some with auricular fibrillation and others with regular sinus rhythm, in a series of experiments which extended in individual cases over periods of from twenty-four to fifty-four weeks.

The results of animal bio-assay methods (frog and cat method) for purified digitalis glucosides are not transferable to man. Their potency must be determined on man directly. Possible reasons for the discrepancies are not discussed.

A method has been described for the assay of digitalis preparations in man, comparing a standard with an unknown preparation in the same individuals.

For the assay of digitalis in man, either RT-T changes in the electrocardiogram in subjects with normal sinus rhythm or ventricular rate changes in those with auricular fibrillation may be used to detect the amount of digitalis action. The two methods yield similar results and reflect the therapeutic potency of digitalis glucosides.

''Digitaline Nativelle'' is about 200 times as potent as digitalis by the cat and frog methods, but 1800 times as potent when the two are compared in man.

It requires from 6 to 12 cat units of digitalis leaf to produce the effects of 1 cat unit of ''Digitaline Nativelle'' by oral administration.

Details of the dosage of ''Digitaline Nativelle'' are discussed. Full digitalization is accomplished by a total of 3 cat units by mouth, whereas for digitalis it requires about 25 cat units.

A safe method has been described for the determination of the ratio of toxic to therapeutic potency of digitalis preparations in man. The results show that this ratio is similar for digitalis leaf and ''Digitaline Nativelle.''

Attention has been called to the marked variability in the strength of U.S.P. XI tinctures of digitalis and to the possibility of the use of purified digitalis materials of more constant potency which may require no animal bio-assay.

AUTHORS.

Miller, Edgar R.: Use of Heparin in Treating a Case of Subacute Bacterial Endocarditis With Patent Ductus Arteriosus. Delaware State M. J. 12: 155, 1940.

An 11-year-old girl with subacute bacterial endocarditis was treated with heparin by the continuous drip method for ten days by transfusion with stored citrated blood and sulfapyridine. The venous clotted time rose the first day from four minutes to four hours twenty-five minutes. She died suddenly on the tenth day of treatment.

Autopsy showed an extensive fresh brain hemorrhage into the lateral ventricle, extending through the third and fourth ventricles to the basal cisternae. There was a patent ductus arteriosus with vegetations or scarring. There was an old mitral valve lesion probably rheumatic in origin; there were fibrous vegetations of subacute bacterial endocarditis. There was evidence that an embolus had been washed off this lesion.

MCCULLOCH.

Stoll, Arthur: The Genuine Cardiac Glucosides. J. Am. Pharm. A. 27: 761, 1938.

This discussion has dealt with attempts to isolate the active principles of drugs in pure form without destroying their natural initial state. Only a few examples in the very specialized and limited field of cardiac glucosides have been given. There are doubtless many other cases where the genuine active principles of drugs are not yet known, and therefore, a vast field for investigation still remains.

AUTHOR.

Corrigendum

The heading of the last abstract on page 646 in the November issue should read **Sosman, Merrill C.: Subclinical Mitral Disease.** J. A. M. A. **115**: 1061, 1940, instead of **Symonds, C. P.: Cerebral Thrombophlebitis.** Brit. M. J. p. 348, Sept., 1940.

American Heart Association, Inc.

RADIO CITY

1790 BROADWAY, NEW YORK, N. Y.

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

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The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

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